SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

2851.

KATONA LAJOS

Mentális egészségtudományok
című program

Programvezető: Dr. Kovács József, egyetemi tanár

Témavezető: Dr. Czobor Pál, egyetemi docens

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

PhD thesis

Lajos Katona

Mental Health Sciences Doctoral School

Semmelweis University

Supervisor:	Pál Czobor, Ph.D
Official reviewers:	Róbert Herold, MD, Ph.D Attila Simor, MD, Ph.D

Head of the Complex Examination Committee:	Dániel Bereczki, MD, D.Sc
Members of the Complex Examination Committee:	György Blaskó, MD, D.Sc Attila Pulay, MD, Ph.D

Budapest
2023

Table of Contents

List of Abbreviations

AC – Anticholinergic Agents

AP – Antipsychotic

BPRS – Brief Psychiatric Rating Scale

CGI – Clinical Global Impression

CI – Confidence Interval

COPD – Chronic Obstructive Pulmonary Disease

DDD – Defined Daily Doses

FGA – First Generation Antipsychotic

HR – Hazard Ratio

ICD – The International Classification of Diseases

IRR – Incidence Rate Ratio

LAI – Long-acting Injectable

LCL – Lower Confidence Limit

MA – Monotherapy Arm

NICE – National Institute for Health & Care Excellence

OAPs – Oral Antipsychotics

OR – Odds Ratio

PA – Polypharmacy Arm

PANSS – The Positive and Negative Syndrome Scale

PDD – Prescribed Daily Doses

QT – a value that is measured on an electrocardiogram (measurements begin from the start of the Q wave to the end of the T wave)

RCT – Randomised Controlled Trials

RCTmeta –Previously Published Meta-analyses Based on RCTs

RD – Risk Difference

RR – Relative Risk

RWD – Real-world Data

RWS – Real-world Study

SE – Standard Error

SGA – Second Generation Antipsychotic

TRS – Treatment Resistant Schizophrenia

UCL – Upper Confidence Limit

1. Introduction

1.1 Background

Real-world data (RWD) have increasingly played an important role in how pharmacotherapies are conducted in real life by physicians, and in the fine-tuning of treatments (Dagenais et al., 2022). Evidence for the effectiveness of a new medication recently approved by regulatory authorities and already available for clinical practice is rather limited. Randomised controlled trials (RCT), which are strictly controlled and regulated by authorities, can only address the efficacy and safety of a new drug candidate to become a medication for human use; RCTs are usually not able to address the effectiveness of a medication in the daily practice (McCutcheon et al., 2020; Nordon et al., 2016).

This thesis is based on two investigations related to the treatment of schizophrenia: (1) an effectiveness study analysing RWD of medications used for the treatment of schizophrenia (Katona et al., 2014); (2) a meta-analysis based on the results of previously published real-world studies (RWSs, which consist of both observational studies and on analyses of health insurance databases or other electronic medical records), and a comparison of the results of this meta-analysis with the results that meta-analyses of RCTs yielded (Katona et al., 2021).

1.2 A summary of clinical aspects of schizophrenia

First, I would like to provide a brief introduction to schizophrenia as this is the indication that our studies focused on. In particular, I am going to focus on the symptoms of schizophrenia that are targeted by pharmacotherapies, on the assessment of their severity, and on the treatment options for the alleviation of these symptoms.

1.2.1 The clinical manifestation of schizophrenia

Schizophrenia is a severe mental disorder with variable course and outcomes: cca. 15% of the patients diagnosed with schizophrenia have a single episode, thus the majority have a disorder with a chronic course with high prevalence of disability and mortality (Bermanzohn et al., 2000; Bitter et al., 2017; Keepers et al., 2020; Leucht et al., 2013; NICE Guideline CG178, 2014). Individuals with schizophrenia can show a wide range of symptoms which can be classified into different domains, for example: positive, negative and cognitive ones (McCutcheon et al., 2020). The most common positive symptoms are hallucinations (mainly auditory) and delusions. The current classification of negative

symptoms is based on the recommendations of the 'Measurement and Treatment Research to Improve Cognition in Schizophrenia' (MATRICS), which led to a consensus conference on negative symptoms. The consensus statement defined five negative symptoms in schizophrenia: blunted affect, alogia, asociality, anhedonia, and avolition (Kirkpatrick et al., 2006). Cognitive symptoms comprise deficits in processing speed, working memory, attention and vigilance, verbal learning, reasoning and problem solving, and social cognition. Patients with schizophrenia often experience episodes (also called as 'Schub') when positive symptoms seriously compromise everyday functioning, but there are also periods of remissions with symptomatic and often also with functional improvement (McCutcheon et al., 2020). In general, positive symptoms have a relative predominance up to middle-late adulthood, while negative symptoms develop slowly over lifetime and are more prominent in the later part of life (McCutcheon et al., 2020). Partial or even complete lack of insight (also called anosognosia) is also one of the specific symptoms in subjects suffering from schizophrenia (Lehrer & Lorenz, 2014). Both the acute symptoms and the relapses of schizophrenia can be controlled to some extent with various therapeutic interventions.

Subjects with schizophrenia not only have some of the symptoms listed above but it is highly likely that they also have psychiatric comorbidities such as anxiety disorders, posttraumatic stress disorder, obsessive-compulsive disorder, depression, and substance use disorder. The prevalence of these comorbidities is higher in schizophrenia as compared to the general population. It is important to highlight that psychiatric comorbidities in schizophrenia are so common that they might be considered being integrated in the disorder itself (Buckley et al., 2009). Patients not only have higher rates of psychiatric comorbidities, but also have multiple physical health problems e.g., cardiovascular diseases, infections, constipation, dementia, Parkinson's disease, diabetes, chronic pain, epilepsy, COPD, dyspepsia, liver disease and irritable bowel syndrome (Smith et al., 2013). Due to the above discussed complex manifestation of schizophrenia, mental and somatic health problems interact to cause more frequent and/or prolonged hospitalisation, poor quality of life and an increased mortality (Bitter et al., 2017; DE Hert et al., 2011a; DE Hert et al., 2011b; Langan et al., 2013). Finally, it is also important to note that the rate of suicide is significantly higher in schizophrenia as compared to the general population (Correll et al., 2022).

1.2.2 The measurement of symptom severity in schizophrenia

Due to the wide range of symptoms and the nature of schizophrenia itself, the assessment of the severity of psychopathological symptoms is a challenging task. To overcome this issue, physicians can potentially use standardised rating scales such as the Positive and Negative Syndrome Scale (PANSS) (Bell et al., 1992; Kay et al., 1987, 1988, 1989), the Brief Psychiatric Rating Scale (BPRS) (Overall, 1974), the Clinical Global Impression Scale (CGI) (Guy, 1976; Haro et al., 2003).

The PANSS is one of the most commonly used psychopathological rating scale for the measurement of the symptom severity of subjects suffering from psychotic behaviours and experience, occurring in schizophrenia (Lim et al., 2021). The PANSS assessment is conducted via an interview with the subject and takes approximately 45 minutes to complete. There are three blocks of items that the scale includes: (1) a positive subscale with 7 items, (2) a negative subscale with 7 items, and (3) a general psychopathology subscale with 16 items. While PANSS is psychometrically established rating scale, it is important to note that the scale, and the psychometric rating scales in general, are not frequently used in everyday clinical practice (Østergaard et al., 2017).

1.2.3 The treatment of schizophrenia

The principal goal in the treatment of schizophrenia is to ease the symptoms and to reduce the chance of relapses (Keepers et al., 2020; Leucht et al., 2013; NICE Guideline CG178, 2014). The "gold standard" in the treatment of schizophrenia is the use of antipsychotic medications (AP). There are two main classes of APs: first-generation antipsychotics (FGA) and second-generation antipsychotics (SGA). As suggested by their names, FGAs represent the older class of antipsychotics compared to SGAs. To briefly summarise the differences between the two classes, FGAs are efficacious in alleviating the positive symptoms of schizophrenia. SGAs are efficacious in reducing both positive and negative symptoms of the disease (Lally & MacCabe, 2015). Some other differences will be discussed later in this chapter.

There are basically two pillars of the successful treatment: (1) subjects need to maintain a good relationship with their psychiatrists by having visits on a regular basis, and (2) they also need to adhere to their treatment, by taking the oral AP medications each day with no major gaps. In addition to the oral APs, there are also long-acting injectable (LAI) APs (also called LAI APs) for use, which can be administered by injection from two-

week to 6 months intervals (Blair, 2022; Johnson, 2009). The main purpose to treat subjects with LAI AP medications is that some patients tend not to take oral APs as regularly as prescribed, or even do not take the medications at all, thereby exhibiting a poor adherence to oral medications (Kaplan et al., 2013).

There are many pitfalls to the successful treatment of schizophrenia, including the limited efficacy on negative symptoms and cognitive impairments (Czobor & Bitter, 2022). Moreover, AP medications may have a wide range of side effects (Iversen et al., 2018; Muench & Hamer, 2010; Stroup & Gray, 2018) such as antihistamine effect, antiadrenergic effect, extrapyramidal syndrome, anticholinergic effect, diabetes, obesity, hypercholesteremia, hypertriglyceridemia, hyperprolactinemia, impotence, liver damage, allergies, epilepsy, QT prolongation, arrythmia, increased risk of cardiovascular events, or even sudden death. Specifically, high potency FGAs generally have a higher affinity for the dopamine receptors, and due to this, they frequently cause extrapyramidal side effects through the blockade of the dopamine receptors. SGAs usually have a lower affinity to the dopamine receptor but can block serotonin receptors. As a result of this, SGAs may be associated with lower risk of extrapyramidal side effects, but might cause different side effects such as change in the level of cholesterol and/or triglyceride, weight gain, as well as the development of diabetes.

Taken together, due to the adverse events of APs and the lack of patients' insight with respect to their disease it is a real challenge for psychiatrists to treat subjects with schizophrenia. More importantly, subjects with inadequate or no treatment, continue to evidence significant positive and negative symptoms, which might lead to a poor quality of life for them (Eack & Newhill, 2007), impacting not only the subjects but placing a major burden on relatives' and caregivers' life.

1.2.4 Treatment resistant schizophrenia

Even though APs have been available for treatment for many decades and the number of individual APs have been increasing in the market, there remain subjects with symptoms which cannot fully be treated. These patients are classified into the class of treatment resistant schizophrenia (TRS). TRS is defined as the presence of symptoms (which are in the majority of cases positive symptoms) despite of 2 or more courses of treatments with APs except of clozapine applied in monotherapy (i.e., AP is given in adequate dose and duration, with adherence documented) (Howes et al., 2017). The prevalence of TRS is

approximately 34% of patients with schizophrenia (Demjaha et al., 2017; Lally et al., 2016; Samara et al., 2019). Once TRS has been established, the recommendation is to switch to clozapine treatment. Based on current guidelines, if despite the use of clozapine, a subject's symptoms still persist (i.e., TRS), psychiatrists are allowed to use more than 2 APs in parallel, i.e., apply AP polypharmacy (Lähteenvuo & Tiihonen, 2021).

1.3 Randomised Controlled Trials

In general, RCTs have a fundamental role in the development of medications, allowing to gain a comprehensive knowledge about the efficacy and safety of an investigational medicine (Bull, 1959; White Junod, 2008). Even though RCTs are very important and cannot be circumvented in clinical drug development, they cannot address all questions which typically arise later in the clinical practice. Specifically, RCTs in the pharmacological treatment of schizophrenia might have a limited ability to represent the real-world patient population in many aspects. In the pivotal RCT studies, for example, men are over-represented; the range of age of subjects recruited is limited (usually from 18 to 55 years); the presence of comorbidities can be a cause for exclusion from the study; subjects with a limited ability to communicate, or with violent or suicidal behaviour cannot be eligible to be involved in the study; typically, only a rather limited number of subjects are recruited; the study period is usually not longer than 6 months; and finally, the follow-up of subjects after the end of study is scarce. The study endpoints used in RCTs are frequently simplified, and are not always suitable to measure major clinically important parameters such as adherence, occurrence of comorbidities due to the treatment. Due to the fact that the sample size is limited (e.g., typically less than 300 subjects in each study arm) and the study period is short in RCTs, the chance to detect rare side effects is very low.

It would not be fair to discuss only the limitations of RCTs, as of course they also have major strengths, such as random assignments of subjects to trial treatment arms; double-blind setting; and the possibility to acquire detailed clinical information on the subjects.

It is important to note that in RCTs, in order to investigate the efficacy of an investigational medicine in patients with schizophrenia, the PANSS rating scale is widely used. Specifically, in the majority of RCTs, the primary endpoint is the change from baseline in PANSS total score, along with the measurement of each of the subscale or factor scores of PANSS as part of the secondary endpoints. These studies are conducted

typically to support the investigational medicine developed by pharmaceutical companies in order to receive authorisation and reimbursement from regulatory authorities and insurance agencies, respectively. From a scientific point of view, it is favourable that the effect of investigational medicine is measured on a continuous scale (PANSS) in RCTs, but it still remains a question how to generalise the results of such measurement to real life. It is important to note that disease specific rating scales (please see section 1.2.2) are not frequently used in everyday clinical practice (Østergaard et al., 2017).

1.4 Regulatory approval of a new medication

Pharmaceutical companies present all data from previously conducted RCTs to provide robust evidence for efficacy and safety of their drug for authorities when applying for marketing authorisation. Before a drug is approved for human use, regulatory authorities based on the results of RCTs need to assess whether the benefit of a new treatment significantly exceeds the harm it can potentially cause (i.e., side effects). Even if the number of RCTs included in a pooled analysis can, for example, be more than 10, the total number of subjects exposed to the new medication usually still remains rather limited, and the number of treatment arms may also remain very limited. Furthermore, the most typical approach is to compare the efficacy and safety profile of a new drug against placebo. RCTs with active control arm involving one of the APs which have already been available on the market are scarce. Due to these limitations, authorities are not always in a position to make an optimal decision with respect to whether a new drug is suitable for use in real-world patient populations. Authorities might not have evidence whether a new AP is as effective and as safe as other APs that have already been widely used.

1.5 Observational Studies

When a new AP medication becomes available in the market, it will be administered to many subjects who may have comorbidities, receive various other drugs, and/or can take APs in polypharmacy. They may also fall outside of the age range of participants who were involved in RCTs, and cannot always be compliant or follow the instructions written in the summary of product characteristics.

As mentioned briefly above, a treatment that has previously been shown to be effective in RCTs may not be sufficiently effective under real-life conditions, as not all potential drug-drug interactions could be investigated at the stage of Phase 1-3 studies. In addition,

some of the side effects become apparent only after the new medication has been placed on the market. This is particularly true for the rare but serious side effects that are not detected in the relatively small samples and due to the short observation periods of pivotal RCTs. Thus, effectiveness cannot be measured with sufficient accuracy in RCTs but can rather be assessed in observational studies. Effectiveness can be measured in number of ways in psychiatry, but one of the most widely used endpoints is the all-cause treatment discontinuation, which can be conceived as a composite endpoint. In particular, this endpoint captures the occurrence of multiple events which can trigger treatment discontinuation. Such event may be (but not necessarily limited to) a patient's decision not to take the AP medication further; switching to another AP medication; the initiation of another AP medication in parallel; admission to hospital; or death for any reason.

Of course, observational studies also have pitfalls such as lack of random assignments to study arms; no blinding, i.e., both subjects and physicians know what AP medication subjects take; and finally, a limited range of clinical parameters that are collected in these studies.

1.6 Studies based on analyses of real-world data

Studies that are based on RWD constitute subtypes of observational studies, and they possess both advantages and disadvantages compared to traditional observational studies. Advantages include: a large number of subjects (even a whole population) can be involved; subjects who are unlikely to be included either in observational studies or RCTs (e.g., non-cooperative, only partially able to cooperate or even aggressive subjects) are also available; non-interventional nature, as they have no confounding factors either on subjects or on physicians; and the observational period can be very long, it can even span multiple decades. Disadvantages can be: only a few clinical measures are available for patients; extracting the relevant data requires special techniques of data analysis; there can be confounding factors, which might lead to imbalance between study arms. In terms of implementation of such studies, it is important to note that RWD can be implemented only in a limited number of countries due to non-availability of the relevant data.

Specifically, in some of the countries full population health insurance databases are available to use for research purposes, which makes possible to follow the patient pathways through the entire health system. The records for research purposes have to be coded, thereby not allowing researchers to identify the subjects. Health insurance

databases usually include records for inpatient and outpatient care, as well as for drug purchases.

Studies based on RWD might provide answers to those key questions, related to the treatment of schizophrenia, which cannot be answered, or only partially or conditionally can be addressed in rigorously designed RCTs conducted in a clinical study environment. Let's take an example where RWD can play such a role in answering some of the key questions for practice. Considering the way of how schizophrenia is treated in everyday clinical practice, and how complex and broad-spectrum the symptoms can be, physicians tend to combine different AP medications, rather than to prescribe one of the APs in monotherapy. However, there is not too much scientific evidence in the literature for the efficacy or effectiveness of combination therapies against monotherapy.

To address the question whether the application of polypharmacy has advantages, if any, compared to monotherapy, our research team conducted a full-population non-interventional retrospective-prospective study using the databases of the National Health Insurance Fund Administration of Hungary (Katona et al., 2014).

1.7 RCT or RWS: What should we rather rely on?

Professionals who work in the field of healthcare sector (e.g., pharmaceutical professionals, general practitioners, healthcare planners and economists, specialists and academic scientists) are often divided on whether they have more confidence either in RCTs or RWSs (including both observational studies and those based on database analyses). The ones who trust RCTs highlight the disadvantages of RWSs, and vice versa. As mentioned above, the opinion accepted by many is that the results obtained from RCTs are not generalisable to real-life situations in many cases. Owing to the lack of randomisation and blinding the effects of the confounding factors cannot be estimated, e.g., the subjects assigned to one study arm may not be comparable as to the subjects in the other arm, since they may have very different attributes (e.g., sex, age, type and dose of medications). Due to the lack of data in this field, we decided to empirically investigate whether the results of RCTs and RWSs in schizophrenia are congruent or incongruent with each other. To this end, we first conducted a meta-analysis summarising the results of published RWS, i.e., of observational studies and the ones that were based on the analyses of health insurance databases. Then, we compared the RWS results with the

previously published meta-analyses based on data obtained from RCTs in order to investigate their congruency (Katona et al., 2021).

2. Objectives

2.1 The objectives of first study

The first study aimed to address the question whether the application of antipsychotic polypharmacy has advantages over monotherapy in the treatment of subjects with schizophrenia or schizoaffective disorder by conducting a full-population non-interventional retrospective-prospective study.

The principal outcome measure of the study was all-cause treatment discontinuation defined by the following outcome events: discontinuation of AP medication, switching to another AP medication, initiation of a new concomitant AP medication as add-on therapy, discontinuation of any of the two medications in the PA, hospitalisation to psychiatric ward, or death due to any reason. The secondary outcome measures were psychiatric hospitalisation and mortality, respectively. The main independent variable of the study was the study arm (i.e., monotherapy arm compared to polypharmacy arm).

2.2. The objectives of second study

The second study aimed to investigate the question of how congruent the results of randomised controlled trials and real-world studies are. To accomplish this, we adopted a two-step approach. First, we conducted a meta-analysis of data obtained from real-world settings. Second, we compared the results of this meta-analysis with the previously published meta-analyses of randomised controlled trials. Only those studies (either RWSs or meta-analyses of RCTs) were included in the analyses which were based on the head-to-head comparisons of antipsychotic medications, and the diagnosis of included subjects was schizophrenia or schizoaffective disorder.

Source data for the studies including both RWSs and meta-analyses of RCTs were obtained from the Pubmed database. The queries for selection were run on 25th of April 2020 with no limitation to the date of publication. We only focused on papers published in English. A total of eight selected AP medications were examined in this study. One of them was oral FGA: haloperidol; six were oral SGAs: amisulpride, aripiprazole, clozapine, olanzapine, quetiapine and risperidone; while there was one LAI SGA medication: risperidone.

The study endpoint for the real-world studies was relative risk (RR) of all-cause treatment discontinuation due to any reason. We included only those results which were adjusted for confounders in the original articles. For previously published meta-analyses of RCTs

we used the RR of all-cause treatment discontinuation due to any reason. In case this was not available, the drop out from the RCTs was investigated. If the relative risk was not available in a paper, we used the odds ratio or the hazard ratio.

3. Methods

3.1 First study

3.1.1 Data collection

For the selection of subjects based on antipsychotic dispensation, the study set a three-year period, spanning from January 1st, 2007 to December 31st, 2009 . Patients had to have at least one valid record of AP dispensation and the diagnosis of schizophrenia or schizoaffective disorder in the majority (≥67%) of prescriptions.

The empirical data for the analysis were extracted from the databases of National Health Insurance Fund Administration of Hungary. In the final analysis set, 14 individual AP medications were included. Out of the 14 APs, two were oral FGA medications: haloperidol and zuclopenthixol; seven were oral SGAs: amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone; four were LAI FGAs: flupentixol, fluphenazine, haloperidol and zuclopenthixol; and one was a LAI SGA: risperidone.

Our respective aim was to compare the above set of medications by defining two parallel study arms: (1) a monotherapy arm (MA), based on switching to a new AP medication after >60 days of initial AP monotherapy; and (2) a polypharmacy arm (PA) with two AP medications, based on the addition of a second AP medication to the existing one, which was taken >60 days as an initial monotherapy. The principal outcome measure of the study was all-cause treatment discontinuation. The secondary outcome measures were psychiatric hospitalisation and mortality, respectively. The main independent variable in the analysis was the study arm (MA or PA).

Eligible patients in MA were included in the analyses if they continued to receive the assigned monotherapy for >60 days; and they were included in the PA if the combined treatment with the two AP medications continued for >60 days. The reason of applying this criterion was to exclude transient polypharmacies and to achieve an equal baseline condition for both arms.

3.1.2 Statistical models

The Kaplan-Meier model for survival analysis was used to determine the median time to treatment discontinuation during the one-year observation (follow-up) period. For inferential statistical analysis the Cox proportional-hazards regression model was applied (Cox, 1972). For group comparisons we used the risk ratio statistics (hazard ratio, HR).

To compare monotherapy to polypharmacy in terms of treatment effectiveness pairwise comparisons were applied: each AP that was used in the MA was compared to those polypharmacies which included that specific AP in combination. To account for any potential demographic or clinical differences between the study arms matched-pair analyses with propensity score matching were conducted (Sekhon, 2011). Using this strategy, we performed Cox proportional-hazards regression model for clustered data based on the matched pairs. For mortality analyses, logistic regressions model was applied by incorporating the propensity score in the model as a covariate.

For propensity score calculation, a multivariate logistic regression model was used. The independent variables that we included in the model were as follows: gender, age (using both linear and quadratic terms) and number of days of hospitalisations (psychiatric or other wards, respectively) during the 1-year prior study.

To account for the multiple comparisons, we applied Hochberg's correction in the inferential statistical comparisons in order to avoid alpha inflation (Hochberg, 1988). All statistical significance tests were two-sided. Statistical analyses were performed with R-software version 2.9.1 (R Development Core Team, 2009).

3.2 Second study

3.2.1 Data collection

The source data for the second study was the Pubmed database. The queries for the selection of publications were executed on 25th of April 2020, with no limitations to the date of publication. We only focused on those studies which were published in English.

3.2.2 The queries for selecting publications

3.2.2.1 Definitions of RWSs queries

There were three separate queries (as listed below) run in Pubmed to identify publications for the potential inclusion of the meta-analysis:

Query 1 (Q1): antipsychotic*[Title/Abstract] AND ((real*[Title/Abstract] AND world*[Title/Abstract]) OR nationw*[Title/Abstract]) AND schizophren*[Title/Abstract] AND (effectiv*[Title/Abstract] OR discont*[Title/Abstract]);

Query 2 (Q2): schizophren*[Title/Abstract] AND discont*[Title/Abstract] AND observational[Title/Abstract]; and

Query 3 (Q3): schizophren*[Title/Abstract] AND discont*[Title/Abstract] AND claim*[Title/Abstract].

The queries resulted in a total of 135, 69 and 36 articles, respectively, for the Q1, Q2 and Q3. After the merge of them, the duplicates were removed resulting in 224 unique articles.

3.2.2.2 Definitions of RCTs query

A query with keywords listed below was applied in Pubmed in order to identify relevant publications of meta-analyses for the potential inclusion based on RCTs: schizophren*[Title/Abstract] AND antipsychotic*[Title/Abstract] AND meta-analysis[Title/Abstract] AND (clinical[Title/Abstract] OR randomi*[Title/Abstract]) AND (trial*[Title/Abstract] OR study[Title/Abstract] OR studies[Title/Abstract]).

After the run of the above query, we identified a total of 459 publications with no duplicates.

3.2.3 Statistical model

For the meta-analysis, we estimated the pooled effect size for each AP pair compared by using a normal mixture model with random effect. The estimated relative risks and their corresponding standard errors (SE) were used as input data based on individual publications for the meta-analysis. All analyses were conducted using the SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC). For further details of statistical model, please see original publication (Online Supplementary Information [Appendix 3]).

We only included those AP pairs in the analyses which were investigated and compared in at least two real-world studies. To examine the robustness of our pooled estimates, we separately examined those AP comparisons where three or more individual study results were available for the analysis.

In the first step in our analysis, we categorised each AP comparison using two approaches based on: (1) whether the pooled meta-analytic estimate was statistically conclusive ($p<0.05$), and (2) whether this evidence appeared consistently in all individual studies. Consistency was defined as the individual study outcomes pointing always in the same direction with respect to their effect size estimate. Each of the AP comparisons was classified into 3 categories as follows:

- statistically conclusive and consistent;
- statistically conclusive but inconsistent;
- neither statistically conclusive nor consistent.

As for the majority of AP comparison only one or two meta-analytic summaries based on RCTs were available in the literature, we selected one primary and, whenever available, one secondary benchmark for comparisons. To consider the result of an RCT meta-analysis as benchmark for a given AP comparison, we reviewed all individual RCTs included in the RCT meta-analysis. If the majority of RCTs was included in both meta-analyses, we used the meta-analyses which (1) were published more recently and/or (2) incorporated a larger number of RCTs. To learn more about the selection process, please see original paper (Online Supplementary Information [eTable 1, Appendix 4]).

In the second step of our investigation, we examined the congruency of the RWS estimates with RCT meta-analytic benchmark(s) for each of the comparisons where results were available. We defined congruency as the correspondence between the sign (i.e., direction) of the pooled effect size estimate from the RWS and the benchmark of RCT meta-analysis. Our presentation of the respective results was organised by using the presence/absence of statistically conclusive results in the RWSs. Based on these criteria, the AP pairs were classified as follows:

- RWS statistically conclusive and show congruency with RCT meta-analysis;
- RWS statistically inconclusive but show congruency with RCT meta-analysis;
- RWS statistically conclusive with incongruence with RCT meta-analysis;
- RWS statistically inconclusive and incongruent with RCT meta-analysis.

It is important to note that for a number of AP comparisons congruency could not be investigated as no RCT meta-analysis was available in the literature.

4. Results

4.1 The results of first study

4.1.1 Patients' selection process

The patient flow for the study is depicted in Figure 1. As shown by the figure, the total number of subjects who received at least one dose of AP medication during the patient selection period and had a majority (defined as ≥67% of all APs purchases) in ICD diagnostic code with schizophrenia or schizoaffective disorder (F2X ICD) was 93,337. The cumulative number of days being on either monotherapy or polypharmacy were 83% and 17% of all days, respectively. Based on the 60 days criterion for the monotherapy a total of 72,008 patients were eligible for an assignment for inclusion to the MA or PA of the study. We note that 70% of this population had stable monotherapy for more than 90 days.

The MA or PA criteria were met by 14,150 patients. The main reason for patients for not qualifying for the study (n=57,848) was that there were a high proportion of patients with no subsequent AP therapy following the end of the at least 60-day monotherapy period, which constituted a principal requirement for exclusion. Specifically, for about 86% of individuals in the attrition set, patients either had periods of time taking no APs for more than 60 days (exceeding the 60 days grace period) or there were no more records for analysing the data within the study period (January 1st, 2007 to December 31st, 2009). There were multiple reasons behind the remaining 14% of the attrition, including hospitalisation, death, and polypharmacy with more than 2 APs. Polypharmacy with >2 APs occurred in approximately 2% of the cases.

The final set of 14,150 patients who were selected either for MA or PA had a total of 21,419 treatment sequences that would qualify them to enter study. To minimise the number of censored patients and to perform a quasi-randomisation, for each patient we selected the earliest occurrence of the qualifying event (i.e., the start of treatment sequence where eligibility was achieved).

Three medications were not included in the analyses: in case of sertindole and zotepine the number of available patients were rather low for the analysis, and in case of paliperidone, the treatment was primarily prescribed only in the last year of the study period. Overall, 14 individual medications with 13,381 patients were included in the study: MA=5,480, PA=7,901. The distribution of patients according to specific

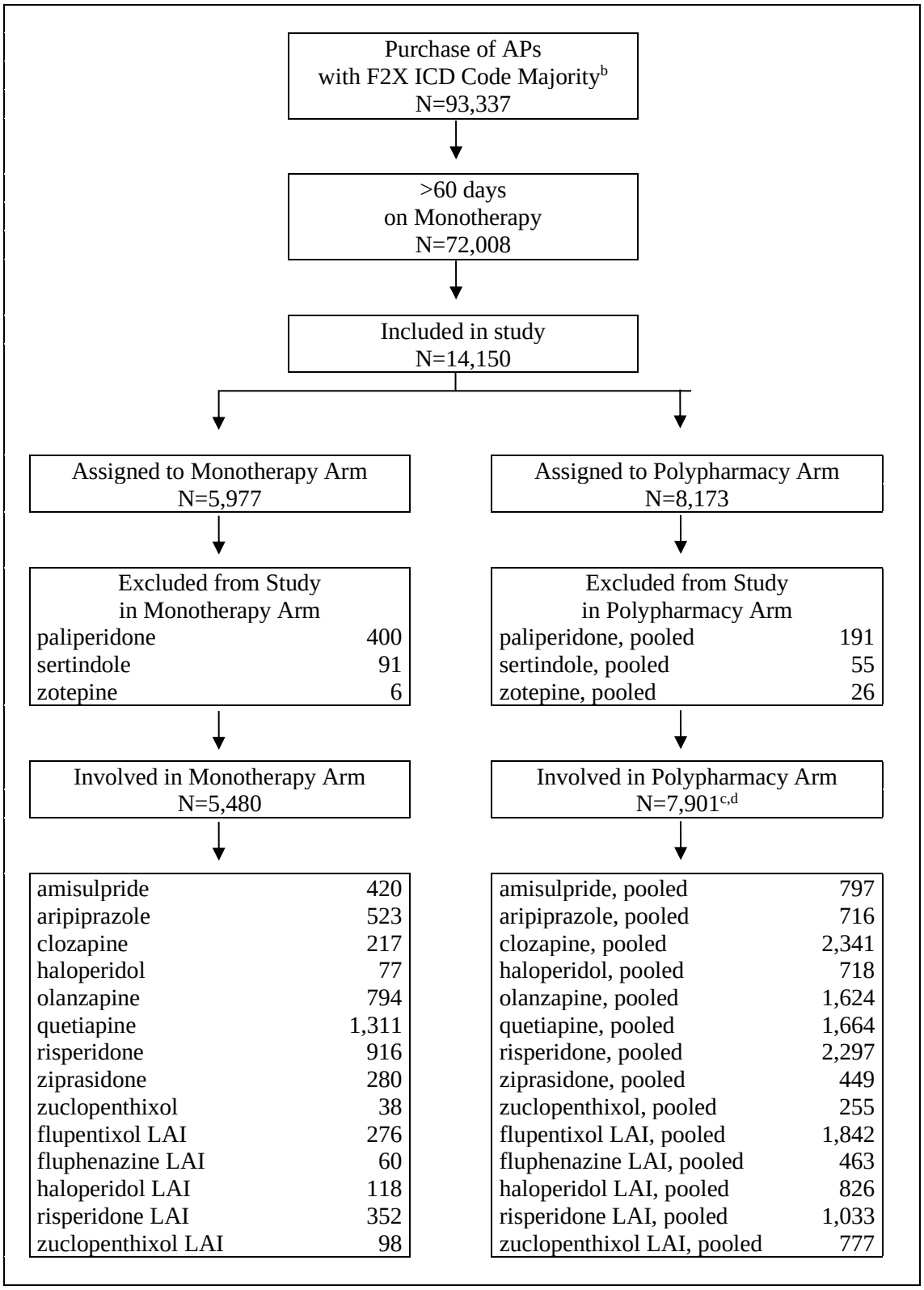

Figure 1: Study Flow Chart[a]

[a] This is a modified version of the figure published in the original paper as Figure 1 (Katona et al., 2014), changing the keyword of "depot" to "LAI".

[b] Majority (≥67%) in ICD diagnostic code with a schizophrenia diagnosis (F2X ICD) over all antipsychotics purchases.

[c] Number of unique patients.

[d] Patients in the individual polypharmacy groups in the box below are included with each of the two medications combined (e.g., a patient receiving a combination of risperidone + clozapine is countered in the 'risperidone, pooled' as well as in the 'clozapine, pooled' group since s/he receives both medications).

treatments in the MA is shown in the bottom left part of Figure 1, whereas the analogous numbers for the PA are shown in the bottom right panel.

4.1.2 Demographics

Basic demographic and descriptive data for patients included in the study are provided in Table 1. As the upper part of the table shows, the overall proportion of males in the entire sample was approximately 42%, and the average age was 49.2 years. In terms of hospitalisations, 23% of the sample was hospitalised in psychiatric ward during the year prior to the study. The comparison of the MAs and PAs yielded significant difference for gender, with a slightly higher proportion of males in the polypharmacy arm (PA=45% vs. MA=38%). No significant difference between the two study arms was observed in terms of age; the proportion of patients hospitalised in psychiatric ($p<0.0001$, MA=28%, PA=19%) or other ward ($p<0.0001$, MA=19%, PA=12%) during the year prior to the study differed significantly between the two arms but the difference was modest.

The lower part of Table 1 shows the demographic and descriptive statistics for each of the medications. Specifically, we determined the estimates of prescribed daily doses (PDD), based on all treatment durations including the 60-day grace period, in order to compare our estimates with those of the WHO data that provided the current standards with regard to standard AP prescribing practices (i.e., with defined daily doses, DDD). For the majority of the APs we found a good correspondence with the WHO DDD but there were relevant differences between PDD and DDD for 2 APs: clozapine and oral haloperidol were prescribed in lower daily doses. There are other studies which reported similar doses for clozapine (Bitter et al., 2008; Fleischhacker et al., 1994) and oral haloperidol (Lin et al., 2010; Oosthuizen et al., 2004). Additionally, higher doses

Table 1: Baseline Demographics and Clinical Characteristics[a]

Gender	Age Mean ±SD		%Male		PDD (mg) Median[b] 95% CI		%Prior Hospitalisation (Psychiatric Ward, Prior 12 months)		%Prior Hospitalisation (other than Psychiatric Ward, Prior 12 months)	
pooled	49.2±14.9		42				23		15	
male	45.2±14.4						22		13	
female	52.1±14.7						23		16	
	mono	**poly**	**mono**	**poly**	**mono**	**poly**	**mono**	**poly**	**mono**	**poly**
pooled	49.1±16.2	49.3±14	38	45			28	19	19	12
male	44.5±15.6	45.6±13.6					29	19	17	11
female	51.8±15.8	52.3±13.7					28	19	19	13
Medications										
amisulpride	46.8±15.6	46.8±14	36	47	341 (99-1000)	416 (100-1000)	27	22	21	12
aripiprazole	43.3±14.5	44.4±13.4	35	44	20 (12-38)	23 (13-42)	30	23	14	9
clozapine	46.9±14.6	48.5±13.4	45	48	96 (29-350)	125 (30-400)	32	14	19	9
haloperidol	54.3±16.5	52.5±14.4	38	48	4.2 (1.7-11.7)	4.4 (1.6-10.7)	22	16	25	13
olanzapine	47.8±16.1	49±14.2	39	48	10 (5-23)	11 (5-28)	29	19	19	11
quetiapine	52.3±16.9	51.1±15.6	35	37	214 (41-750)	356 (48-1000)	29	23	22	15
risperidone	51.1±17.3	49.9±15	39	46	3.2 (1.1-7.7)	3.9 (1.1-9.5)	25	20	18	13
ziprasidone	45.3±14.7	48.1±13.9	34	39	100 (43-210)	112 (41-230)	26	17	14	14
zuclopenthixol	49±13.8	47.5±13.5	53	56	32 (9-129)	38 (10-139)	34	16	11	14
flupentixol LAI	50.9±14.2	51.4±12.6	32	37	2.6 (1.9-7.3)	2.7 (1.9-5.7)	29	16	16	12
fluphenazine LAI	51.7±12.6	51.9±12.6	47	49	2.2 (1.3-5.6)	1.8 (1.2-3.9)	13	11	17	11
haloperidol LAI	49.7±14.4	50.7±12.7	51	52	4.1 (3-7.1)	4.0 (2.4-8.9)	25	16	14	11
risperidone LAI	47.7±14.9	46.7±13.9	41	45	2.5 (1.2-4.2)	2.7 (1.4-4.2)	32	28	20	12
zuclopenthixol LAI	47.6±13.3	48±12.4	41	48	10 (6-38)	11 (5-34)	39	24	8	10

[a] This is a modified version of the table published in the original paper as Table 1 (Katona et al., 2014), changing the keyword of "depot" to "LAI".

[b] Predicted Daily Doses (PDD) was computed based on the sum of active ingredients of the medications divided by the estimated total days of treatment value.

were observed for PA than for MA AP medications. This might be attributed to the fact that the likelihood of a ≤60-day pause during the treatment was obviously higher in the MA than in the PA arm.

Regarding prescriber effects, there were no statistically significant difference in the ratio of polypharmacy vs. monotherapy between MA and PA for psychiatrists who contributed prescriptions for subjects included in this study.

4.1.3 Discontinuation of treatment

4.1.3.1 Kaplan-Meier estimates

In order to exclude potential transient polypharmacies (i.e., ≤60 days) and to set equal conditions at baseline between MA and PA, survival functions and ancillary statistics are presented for the period subsequent to the first 60 days in both study arms. Time to all-cause discontinuation based on raw data for each comparison and each study arm is shown in Figure 2. The upper part of Figure 2 displays the mono- and polypharmacy comparisons for each of the 9 individual oral AP medications while the lower part of the figure shows the comparisons for the 5 LAI APs. As indicated by the survival distribution functions, the overwhelming majority of the comparisons for oral APs show the superiority of monotherapy treatments compared to the polypharmacy. Furthermore, with regard to LAI treatments we found a more differentiated picture. In particular, the Kaplan-Meier curves indicate a clear advantage for the monotherapy in case of risperidone LAI. In the case of flupentixol and zuclopenthixol LAI the polypharmacy combinations were associated with a longer time to discontinuation; nonetheless, even with this polypharmacy advantage, in terms of median survival times, combinations of these medications were therapeutically inferior to other polypharmacy combinations. Finally, for fluphenazine and haloperidol LAI, there were numerical advantages for polypharmacy but the effect did not reach statistical significance.

In addition to the Kaplan-Meier curves, we also compared the MAs and PAs for each of the medications in terms of median time to 50% survival on the given medication. Results of these comparisons are shown side-by-side for each of the medication in the right part of Table 2A. As indicated by the column of differences in days of all-cause treatment discontinuation, for 3 of the comparisons (aripiprazole, olanzapine and quetiapine) the polypharmacy strategy resulted in major loss of effectiveness of AP treatments (between 3 and 4.5 months of survival duration on the PA as compared to the MA). In addition, in

3 of the 9 comparisons (amisulpride, risperidone and ziprasidone) the monotherapy strategy resulted in an approximately 2 months of advantage compared to polypharmacy in terms of survival on the treatment until discontinuation due to any reason. With regard to LAI medications, in comparisons where polypharmacy showed an advantage over monotherapy the most substantial difference that we found was approximately 1 month (flupentixol and zuclopenthixol). We note that risperidone LAI showed a considerable loss of effectiveness when used in combination (approx. >3.5 months).

4.1.3.2 Patient dispositions

In Table 2A on top of the Kaplan-Meier median survival statistics, patient dispositions are also displayed in terms of the following events: rates of changing therapy, psychiatric hospitalisation, treatment discontinuation [pause], death and study completion and the estimations of median time to all-cause treatment discontinuation (including 95% confidence intervals) for each of the APs in both study arms (i.e., MA and PA). The one-year patient disposition data based on Kaplan-Meier estimates indicate that the overwhelming majority of APs applied in monotherapy were still ongoing, with 12% to 42% of the patients (except for flupentixol LAI and zuclopenthixol LAI, which had a rate of 4.6% and 4.8% of ongoing patients, respectively), while for all of the APs applied in polypharmacy the range was between 13% and 28%.

Therapy was changed to another AP medication more frequently in PA compared to MA, while treatment discontinuation (pause) was more prominent in MA. It is in line with the clinical context in which the two different treatment strategies are applied by psychiatrists: if the patient takes two AP medications in parallel, the chance of stopping one of the two APs will be greater than the termination of both of them at the same time.

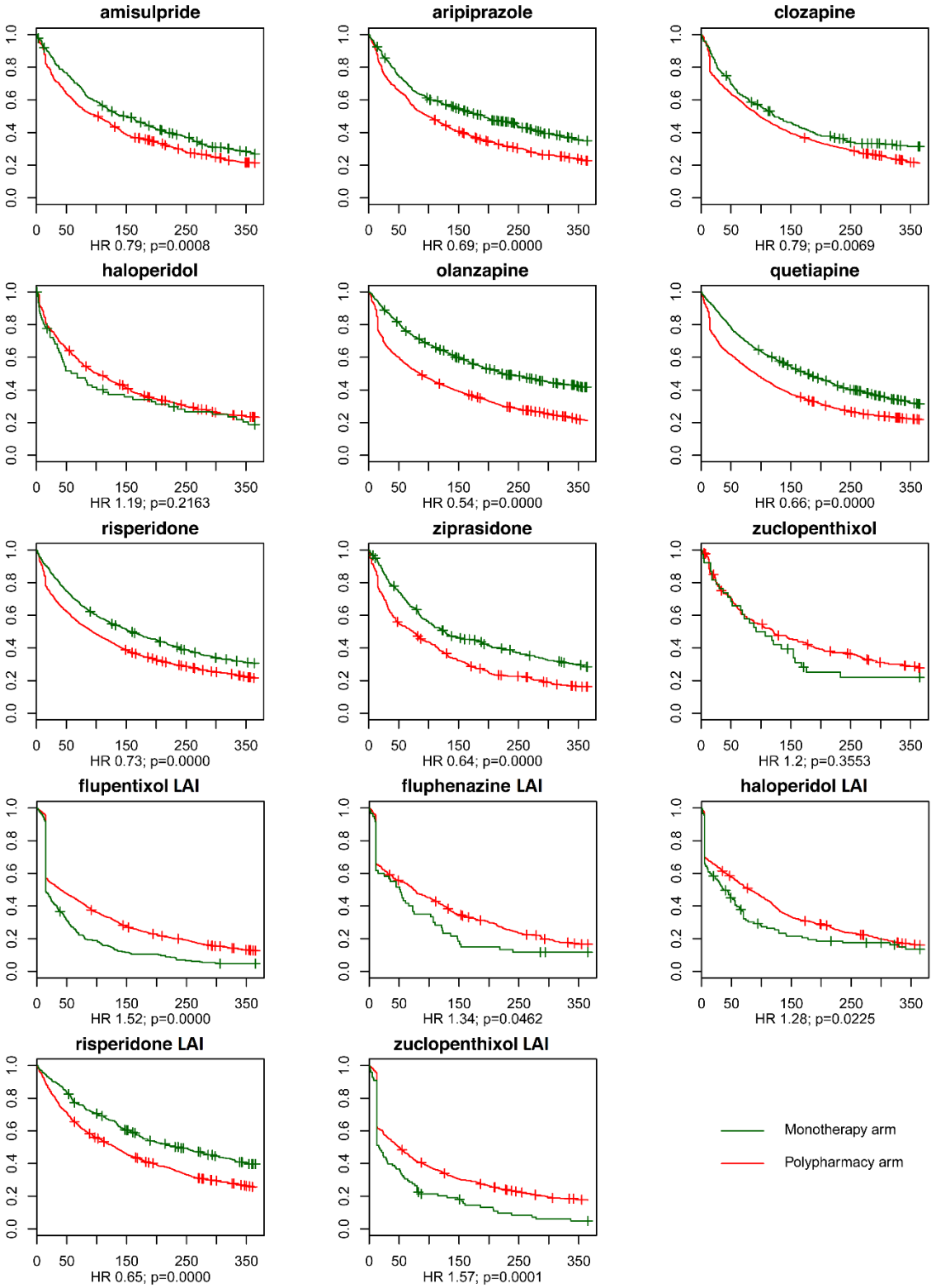

Figure 2: Time to all-cause discontinuation for oral and LAI medications, Kaplan-Meier curves[a,b].

[a] This is a modified version of the figure published in the original paper as Figure 2 (Katona et al., 2014), replacing the keyword of "depot" to "LAI".

[b] Survival curves are estimated on the basis of observed raw data using the non-parametric Kaplan-Meier approach. Survival functions are based on and presented for the period subsequent to the first 60 days in both arms.

4.1.3.3 Cox regression and logistic regression models

The estimates of hazard ratio for all-cause treatment discontinuations and psychiatric hospitalisations, and the estimates of odds ratios for death are shown in Table 2B. For each of the endpoints, both raw and propensity score adjusted estimates – which were determined to correct for baseline differences – are depicted in the Table. In the subsequent text I will only refer to the adjusted estimates, as the raw and adjusted estimates of hazard ratios were consistent with each other for all comparisons.

With regard to all-cause treatment discontinuation (Table 2B, left hand) for oral APs, none of the adjusted comparisons yielded a significant difference in favour of the combinations. There was a statistically significant difference favouring monotherapy for 6 out of 9 comparisons, and no significant difference was found in 3 cases (clozapine, haloperidol and zuclopenthixol). In terms of the pooled results of the Cox proportional hazard model, there was a clear advantage for MA compared to PA (HR=0.68, 95%CI=0.66-0.71). As for the LAI formulation of APs, all of 5 comparisons showed statistically significant difference between the two study arms. Specifically, risperidone LAI applied in monotherapy demonstrated a statistically significant estimate with a reduced likelihood of all-cause treatment discontinuation (HR=0.60). For the rest of the other four cases (i.e., flupentixol LAI, fluphenazine LAI, haloperidol LAI and zuclopenthixol LAI), monotherapy was associated with increased treatment discontinuation (HR=1.35, 1.64, 1.39 and 1.69, respectively); however, it is important to note that the median time to treatment discontinuation was modest in both study arms (i.e., in MA and PA).

In terms of the pooled results for psychiatric hospitalisations (Table 2B, middle part), a more frequent occurrence was present for MA compared to PA, as indicated by the adjusted Cox proportional hazard model that showed a statistically significant difference between the direction of HR based on the pooled data was consistent across all individual comparisons, with two exceptions: oral and LAI formulation of zuclopenthixol.

Table 2A: Outcome Measures of Effectiveness[a,b] – Patient Disposition and Kaplan-Meier Estimates

Medications	%Changing Therapy[c,d]		%Psychiatric Hospitalisation[d]		%Pause[d,e]		%Death[d]		%Completed[f]		Time to All-cause Discontinuation in Days Median 95% CI	
	mono	Poly	mono	poly	mono	poly	mono	poly	mono	poly	mono	poly
amisulpride	24.1	60.8	13.5	6.1	34.5	10.9	1.0	0.8	26.9	21.5	150 (119-184)	101 (80-121)
aripiprazole	21.8	55.1	11.1	7.2	31.8	14.7	0.4	0.2	34.9	22.8	192 (156-245)	100 (81-119)
clozapine	29.8	61.1	9.4	4.7	28.8	12.1	0.5	0.8	31.4	21.3	122 (99-173)	98 (92-107)
haloperidol	28.0	58.9	12.6	5.1	39.2	11.2	1.4	1.6	18.8	23.3	68 (42-147)	101 (86-122)
olanzapine	22.5	63.7	10.1	5.2	24.2	9.3	1.7	0.7	41.6	21.1	222 (192-283)	86 (76-98)
quetiapine	18.4	59.2	13.3	5.5	35.4	12.9	1.5	0.7	31.4	21.8	176 (159-196)	91 (81-100)
risperidone	20.3	59.7	9.3	5.5	37.6	12.6	2.2	0.9	30.5	21.4	157 (139-184)	93 (86-104)
ziprasidone	31.9	64.6	13.6	4.9	24.5	13.5	1.6	0.7	28.4	16.2	127 (100-190)	74 (52-90)
zuclopenthixol	40.4	55.9	2.7	4.1	32.3	11.1	2.7	1.2	21.9	27.7	107 (66-168)	121 (88-175)
flupentixol LAI	26.5	72.0	3.7	3.7	65.2	11.5	0.0	0.3	4.6	12.6	15 (15-24)	39 (31-49)
fluphenazine LAI	28.3	66.2	5.0	3.2	55.0	13.6	0.0	0.5	11.7	16.6	51.5 (15-75)	74 (59-97)
haloperidol LAI	30.6	68.1	6.3	4.6	47.8	10.0	1.8	1.2	13.5	16.1	37 (23-59)	81 (66-97)
risperidone LAI	21.4	56.3	13.5	7.8	23.6	10.0	1.8	0.6	39.7	25.3	237 (180-303)	131 (115-145)
zuclopenthixol LAI	25.1	64.2	5.2	5.0	64.9	12.8	0.0	0.4	4.8	17.7	16.5 (13-39)	50 (39-61)

[a] This is a modified version of the table published in the original paper as Table 2 [upper part] (Katona et al., 2014), changing the keyword of "depot" to "LAI".

[b] All results presented in the table are computed for the period subsequent to the first 60 days in both arms.

[c] Including switch to or add-on of new medication in the monotherapy arm, or discontinuation either one of two medications in the polypharmacy arm.

[d] Proportion of events leading to discontinuation in set of the patients who prematurely terminated the study period.

[e] No purchase within specified grace period (i.e., 60 days).

[f] Survival rate at the end of study (365 days) based on Kaplan-Meier estimates.

Due to the relatively short (1-year) follow-up period mortality (as the cause of treatment discontinuation) did not occur frequently; the total death events were 69 and 53 for MA and PA, respectively. In PA a lower mortality rate was detected compared to MA. As for the propensity score adjusted estimate, the logistic regression model (Table 2B, right hand) showed a statistically significant overall advantage for PA reducing the likelihood of death (OR=1.62, 95%CI=1.12-2.34).

4.1.3.4 Pairwise comparisons of individual AP medications

For all-cause treatment discontinuation, the outcome of individual AP medications applied in monotherapy and the outcome of their corresponding pairs of AP polypharmacies (e.g., amisulpride monotherapy compared to the combination of 'amisulpride+aripiprazole') were compared based on the adjusted results, as shown in Table 3. These detailed results provide information about how the individual pairs of polypharmacies contribute to the pooled findings depicted in Table 2B. Regarding the oral AP medications, it is important to note that olanzapine achieved significantly better results in all 13 pairwise comparisons when it was applied in monotherapy as opposed to polypharmacies. For aripiprazole, quetiapine and risperidone, MA was superior over PA and reached significant difference for the majority of comparisons, while for amisulpride and ziprasidone numerical advantages were detected although the difference did not reach statistical significance due to the limited statistical power. As for the LAI formulation of first-generation AP medications, an advantage of PA over MA was found. Those combinations where the difference was statistically significant are highlighted in green in Table 3 of the original paper (due to the extent of the table, it was not presented in this thesis) (Katona et al., 2014). With regard to the only one LAI formulation of second-generation APs included in this analysis, a statistically significant superiority of risperidone was found for MA over PA for all the combinations applied in clinical practice for 10 or more subjects (for 7 of 7 medications).

Table 2B: Outcome Measures of Effectiveness[a,b] – Inferential Statistical Analyses

Medications	Hazard Ratio Estimates for All Cause Discontinuation[c]				Hazard Ratio Estimates for Discontinuation Due to Psychiatric Hospitalisation[c]				Odds Ratio Estimates for Discontinuation Due to Death[d]			
	Raw		Adjusted[e]		Raw		Adjusted[e]		Raw		Adjusted[f]	
	HR	p	HR	p	HR	p	HR	p	OR	p	OR	p
amisulpride	0.79	0.0008*	0.77	0.0000*	1.82	0.0030*	1.91	0.0066	1.27	0.7145	1.16	0.8218
aripiprazole	0.69	0.0000*	0.64	0.0000*	1.26	0.2507	1.21	0.3970	2.74	0.4102	3.67	0.2923
clozapine	0.79	0.0069*	0.99	0.7682	1.79	0.0193	1.96	0.0001*	0.63	0.6574	0.71	0.7377
haloperidol	1.19	0.2163	1.07	0.4557	2.83	0.0056	2.50	0.0148	0.85	0.8734	0.76	0.7949
olanzapine	0.54	0.0000*	0.54	0.0000*	1.34	0.0726	1.39	0.0550	2.25	0.0533	1.87	0.1431
quetiapine	0.66	0.0000*	0.69	0.0000*	1.78	0.0000*	2.19	0.0000*	2.17	0.0525	1.73	0.1806
risperidone	0.73	0.0000*	0.73	0.0000*	1.37	0.0301	1.55	0.0005*	2.54	0.0043	2.05	0.0325
ziprasidone	0.64	0.0000*	0.62	0.0000*	2.07	0.0085	2.33	0.0067	2.15	0.3173	2.67	0.2048
zuclopenthixol	1.20	0.3553	1.42	0.1276	0.76	0.7893	0.59	0.6640	2.27	0.4827	2.82	0.3871
flupentixol LAI	1.52	0.0000*	1.35	0.0000*	1.68	0.1282	1.35	0.3684	n/a[g]	n/a	n/a	n/a
fluphenazine LAI	1.34	0.0462	1.64	0.0000*	1.93	0.3016	6.34	0.0011	n/a	n/a	n/a	n/a
haloperidol LAI	1.28	0.0225	1.39	0.0000*	1.89	0.1238	1.14	0.7026	1.57	0.5697	1.57	0.5729
risperidone LAI	0.65	0.0000*	0.60	0.0000*	1.39	0.0844	1.77	0.0051	2.97	0.0610	2.81	0.0762
zuclopenthixol LAI	1.57	0.0001*	1.69	0.0000*	1.57	0.3462	0.62	0.3458	n/a	n/a	n/a	n/a
pooled	0.71	0.0000	0.68	0.0000	1.66	0.0000	1.69	0.0000	1.89	0.0005	1.62	0.0100

* Statistically significant differences after Hochberg correction ($p<0.05$).

[a] This is a modified version of the table published in the original paper as Table 2 [lower part] (Katona et al., 2014), changing the keyword of "depot" to "LAI".

[b] All results presented in the table are computed for the period subsequent to the first 60 days in both arms.

[c] Hazard ratios ware estimated based on the Cox proportional hazard regression model.

[d] Odds ratios ware estimated based on logistic regression model.

[e] Hazard ratio and p-value was adjusted based on propensity scores for matched-pair data.

[f] Odds ratio and p-value was adjusted based on propensity scores, used as a covariate in the model.

[g] n/a, odds ratios and p-values were not computed with event count of <1.

4.1.3.5 Sensitivity analyses

In the main analysis, the total number of days of treatment with the initial assignment (either to mono- or polypharmacy) was defined as a sum of sequential, concatenated periods of days of treatments, including the potential grace periods that were allowed for up to 60 days. As sensitivity analyses, a 30- and a 90-day cut-off, respectively, was also applied. These analyses indicated that the findings remained essentially unchanged as compared to the default threshold criterion of 60 days.

Finally, as the main analysis had a focus on subjects with F2X diagnoses of ICD (i.e., schizophrenia or schizoaffective disorder), a subsidiary analysis was conducted wherein only those subjects were selected who had a majority of the core diagnosis of schizophrenia. We investigated if our findings were also replicable in this subpopulation. Specifically, the sample size for the target population of patients with schizophrenia diagnosis (F20 of ICD) was 3,394 in the monotherapy arm, and 6,090 in the polypharmacy arm. After repeating the primary analysis on this more limited population, our main results remained essentially unchanged (Table 3).

Table 3: Sensitivity Analysis for Outcome Measures of Effectiveness using F20 Majority as Inclusion Criteria[a,b]

Medications	Hazard Ratio Estimates for All Cause Discontinuation[c]				Hazard Ratio Estimates for Discontinuation Due to Psychiatric Hospitalisation[c]				Odds Ratio Estimates for Discontinuation Due to Death[d]			
	Raw		Adjusted[e]		Raw		Adjusted[e]		Raw		Adjusted[f]	
	HR	p	HR	p	HR	p	HR	P	OR	p	OR	p
amisulpride	0.82	0.0221	0.78	0.0013*	1.77	0.0145	1.86	0.0115	1.44	0.6190	1.39	0.6590
aripiprazole	0.68	0.0000*	0.65	0.0000*	0.91	0.6750	0.81	0.4595	n/a	n/a	n/a	n/a
clozapine	0.90	0.2868	1.02	0.6008	1.51	0.1984	1.23	0.2691	0.83	0.8560	1.08	0.9422
haloperidol	1.35	0.0697	1.52	0.0001*	3.44	0.0037*	5.99	0.0000*	1.28	0.8199	1.01	0.9962
olanzapine	0.51	0.0000*	0.49	0.0000*	1.20	0.3394	1.13	0.5142	2.87	0.0425	2.37	0.1024
quetiapine	0.79	0.0001*	0.77	0.0000*	2.08	0.0000*	2.16	0.0001*	3.36	0.0277	2.66	0.0822
risperidone	0.74	0.0000*	0.71	0.0000*	1.41	0.0572	1.15	0.3308	2.02	0.1192	1.51	0.3774
ziprasidone	0.64	0.0001*	0.59	0.0000*	1.52	0.1999	2.10	0.0645	0.64	0.7030	0.70	0.7570
zuclopenthixol	1.14	0.5367	1.31	0.2627	n/a[g]	n/a	n/a	n/a	2.97	0.3800	3.43	0.3282
flupentixol LAI	1.70	0.0000*	1.53	0.0000*	2.11	0.0528	1.67	0.0925	n/a	n/a	n/a	n/a
fluphenazine LAI	1.30	0.1115	1.70	0.0000*	1.55	0.5672	2.29	0.2364	n/a	n/a	n/a	n/a
haloperidol LAI	1.32	0.0327	1.59	0.0000*	1.47	0.4679	1.04	0.9298	1.72	0.4915	1.74	0.4874
risperidone LAI	0.64	0.0000*	0.59	0.0000*	1.53	0.0538	1.77	0.0107	3.59	0.0723	3.56	0.0756
zuclopenthixol LAI	1.44	0.0047*	1.45	0.0000*	1.45	0.4883	0.68	0.4511	n/a	n/a	n/a	n/a
Pooled	0.75	0.0000	0.71	0.0000	1.59	0.0000	1.39	0.0001	1.76	0.0125	1.58	0.0459

* Statistically significant differences after Hochberg correction ($p<0.05$).

[a] This is a modified version of the table published in the original paper as ”Online Supplement for Table 2” (Katona et al., 2014), changing the keyword of “depot” to “LAI”.

[b] All results presented in the table are computed for the period subsequent to the first 60 days in both arms.

[c] Hazard ratios ware estimated based on the Cox proportional hazard regression model.

[d] Odds ratios ware estimated based on logistic regression model.

[e] Hazard ratio and p-value was adjusted based on propensity scores for matched-pair data.

[f] Odds ratio and p-value was adjusted based on propensity scores, used as a covariate in the model.

[g] n/a, odds ratios and p-values were not computed with event count of <1.

4.2 The results of second study

4.2.1 The results of selection process of Pubmed search

4.2.1.1 The results for RWSs

The selection process of RWSs is shown in Figure 3 (left panel). On the first level of selection, 9 articles were excluded as the languages they were published were other than English. On the next level, a total of 58 papers were excluded due to the lack of original empirical data published (i.e., the papers usually represented reviews, meta-analyses, letters, or guidelines). On the third level, we identified 23 studies with a design not meeting the specific criteria of real-world study settings (e.g., they provided no results for unique AP medications; they contained previously published results of randomised controlled trials, surveys; and some of them represented theoretical papers, or studies about dose reduction). On the fourth level, we excluded 6 articles because their study population was other than 'schizophrenia or schizoaffective disorders'. On the next level, 70 publications were excluded due to the lack of required endpoint used (i.e., time to all-cause discontinuation due to any reason). On the sixth level, we identified 11 studies for exclusion because they did not use the specific endpoint measures (i.e., neither relative risk, nor odds ratios or hazard ratios). On the next level, we excluded 31 papers because they did not have specific head-to-head comparisons of AP medications. On the subsequent level, 4 articles were excluded because their analyses were based on overlapping datasets, and results were also published in other papers, which were included in the current analysis. On the final level, one paper (Mohamed et al., 2009) was excluded because there was no sufficient information with respect to relevant summary statistics for the endpoint (in Figure 3, left panel, with the reason for exclusion listed as 'Other reasons'). Ultimately, at the end of the selection process there was a total of 11 publications identified for the inclusion into our meta-analysis.

4.2.1.2 The results for RCTs

The selection process of RCTs is depicted in Figure 3 (right panel). On the first level, 19 papers were excluded as their languages were other than English. On the next level, we excluded 77 articles as not being meta-analyses. On the third level, we excluded 19 articles as they had study populations other than 'schizophrenia or schizoaffective disorders'. On the next level, there were 302 publications with a trial design which did not meet the requirements of the current meta-analysis (some were not

psychopharmacological studies, e.g., ECT, Transcranial Magnetic Stimulation, physical exercise; or focused on specific safety measures (e.g., metabolic syndromes); or represented network meta-analyses, with no input data on direct pairwise comparisons from individual studies). On the fifth level, we excluded further 17 meta-analyses as they had no head-to-head comparisons of AP medications included in their analyses. On the next level, we excluded 14 meta-analyses as they had no comparisons of those AP medications that we examined in our meta-analysis based on RWSs. Five meta-analyses were excluded on the seventh level due to other reasons (no head-to-head comparison in specific APs, overlapping datasets, no relevant numerical results, excluded site data were incorporated in the source meta-analysis). At the end of the selection process, we identified 6 publications, and during further literature review we found one more paper for inclusion. Therefore, a total of 7 publications of previously published meta-analyses based on RCTs were selected.

4.2.2. Analyses of RWSs

4.2.2.1 Descriptive statistics of selected RWSs

Table 4, which represents a shorter version of the table published in the original paper as Table 1 (Katona et al., 2021), provides a brief description of the studies which were based on the real-world data and were included in this meta-analysis. In terms of the source data of selected studies, 3 of 11 represented observational studies while 8 of them were based on database analysis using electronic medical/health insurance records. For each study, the table displays the list of 8 APs that we focused on (listed in the Objectives), and in a separate column (labelled as 'Control APs') those APs are shown which served as comparators in the original study. The minimum duration of follow-up period of studies was 12 months (n=4). Further details on demographic data (such as number of subjects, gender distribution, mean and standard deviation of age) can be found in Table 1 in the original paper published (Katona et al., 2021).

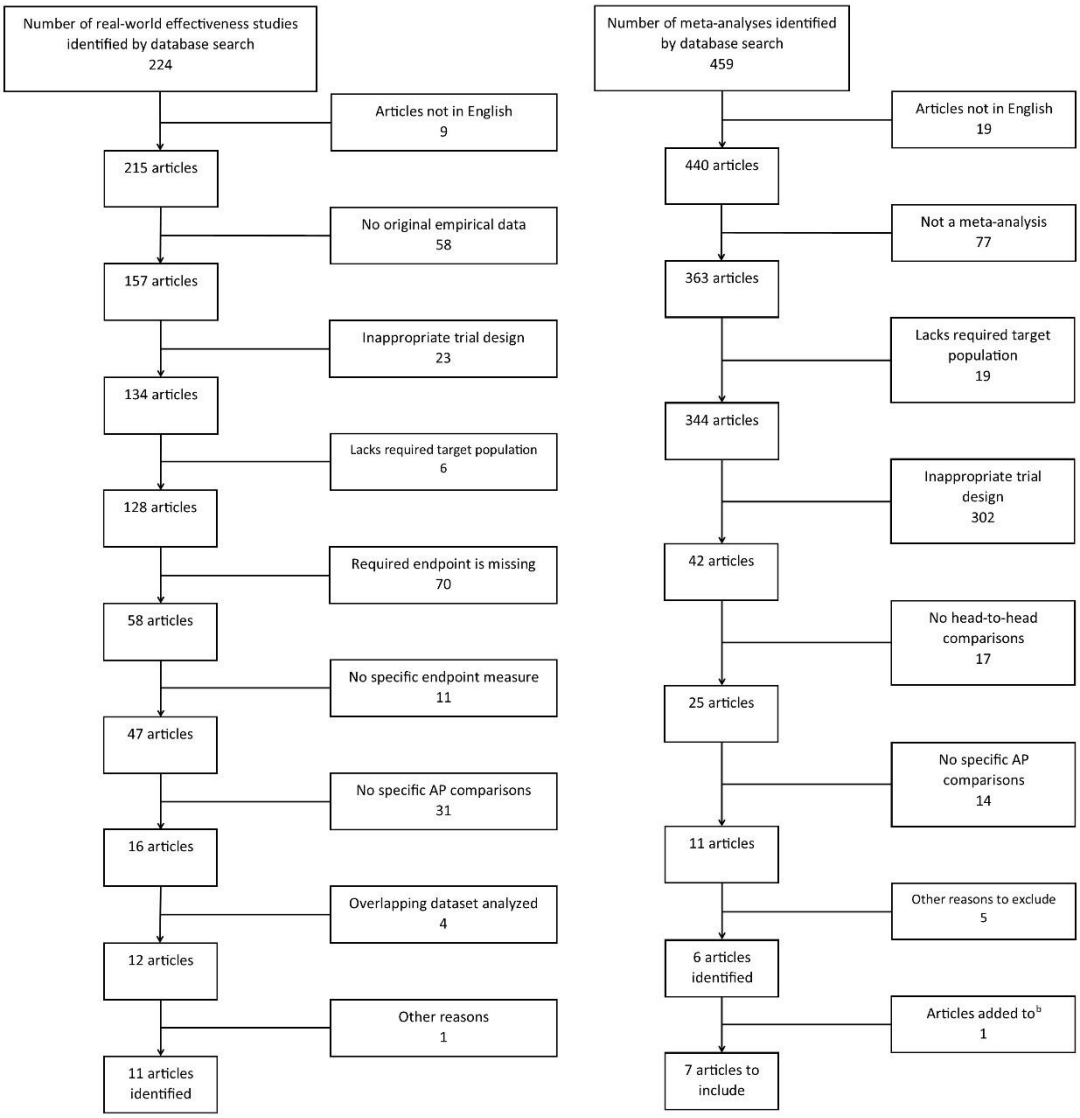

Figure 3: Flow chart of selection process of real-world effectiveness studies (left panel), and previously published meta-analyses based on randomised controlled trials (right panel)[a]

[a] This is a copy of the figure published in the original paper as Figure 1 (Katona et al., 2021).

[b] Article was identified during the review of selected papers: Sampson S, Hosalli P, Furtado VA, Davis JM; Risperidone (depot) for schizophrenia (Review); Cochrane Database Syst Rev 2016. (Sampson et al., 2016)

Table 4: Descriptive characteristics of real-world studies selected for meta-analysis[a]

1st Author and Year of Publication	Study Design and data source	Country where the Study Was Conducted	Follow-up Period (months)	Selected APs Involved in our Meta-analysis	Control APs
Cooper et al., 2005	Population-based cohort study, Quebec health insurance databases	Canada	12	olanzapine, risperidone	olanzapine
Ascher-Svanum et al., 2006	Observational, non-randomized, multisite, prospective, naturalistic study	Various areas in the US	12	clozapine, haloperidol+AC, olanzapine, quetiapine, risperidone	haloperidol +AC
Tiihonen et al., 2006	Prospective cohort study using national central registers	Finland	43.2 (mean)	clozapine, haloperidol, olanzapine, risperidone	haloperidol
Haro et al., 2007	Prospective observational longitudinal study	Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Portugal, Spain and the UK	36	amisulpride, clozapine, olanzapine, quetiapine, risperidone	olanzapine
Kilzieh et al., 2008	Retrospective study, electronic medical records database at a Veterans Affairs Medical Center	US, Veteran Administrations Data	NA	olanzapine, risperidone	olanzapine
Dossenbach et al., 2008	Prospective observational longitudinal study	27 countries across 4 continents	36	haloperidol, olanzapine, quetiapine, risperidone	olanzapine
Tiihonen et al., 2011	Nationwide cohort study, national databases	Finland	24 (mean)	clozapine, haloperidol, olanzapine, quetiapine, risperidone LAI, risperidone	risperidone
Bitter et al., 2013	Nationwide, full-population based, insurance databases	Hungary	12	amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone LAI, risperidone	pairwise
Katona et al., 2014	Nationwide population-based study, insurance databases	Hungary	12	amisulpride, aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone LAI, risperidone	pairwise
Tiihonen et al., 2017	Prospectively gathered nationwide databases	Sweden	68.4 (mean)	aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone LAI, risperidone	olanzapine
Takács et al., 2019	Nationwide population-based study, insurance databases	Hungary	24	amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone LAI, risperidone	risperidone LAI

[a] This is a shortened version of a table published in the original paper as Table 1 (Katona et al., 2021).

4.2.2.2 Meta-analyses of RWS

4.2.2.2.1 Pooled results with two or more RWS datasets available

We included only those AP comparisons in the meta-analysis which had data available from at least two real-world studies. In theory, there could be 28 unique pairwise comparisons based on the 8 APs. Based on the criterion for data availability (i.e., data from at least 2 studies), a total of 25 AP comparisons were identified and included in current meta-analysis. There were 16 (64%) comparisons which showed a statistically significant difference between the two treatments. Regarding the effect sizes, we observed only one large effect size (clozapine-haloperidol, RR=0.33), while for the other 24 comparisons the effect sizes were more of a medium magnitude (RR [or its reciprocal value] between 1.5 and 2). The graphical illustration including numerical results of the individual comparisons are provided in Figure 4a and 4b.

In order to investigate the effectiveness of individual AP medications we had to take the reciprocal values of those RRs which were depicted in an opposite order due to the alphabetical order of pairwise comparisons presented in Figure 4a and 4b. When a reciprocal value was used, it was indicated by an asterisk (*) in this paragraph.

Overall, olanzapine was superior over 5 APs (out of 7 APs compared to) reducing the risk of all-cause treatment discontinuation. These APs with their RRs were as follows: amisulpride (0.69*), aripiprazole (0.88*), haloperidol (0.58*), quetiapine (0.72), and risperidone (0.71). There was no statistically significant difference when olanzapine was compared to clozapine and risperidone LAI. Risperidone LAI showed superiority over 5 APs (out of 6 comparisons). APs with corresponding RRs were: amisulpride (0.66*), aripiprazole (0.79*), clozapine (0.74*), quetiapine (0.75*), and risperidone (0.6). As mentioned above, there was no significant difference between risperidone LAI and olanzapine. Regarding aripiprazole, it was superior in 2 comparisons (out of 6) reducing the risk of all-cause treatment discontinuation. These APs with their RRs were as follows: amisulpride (0.78) and risperidone (0.83). While aripiprazole was inferior to olanzapine and risperidone LAI. Quetiapine was superior over 2 APs (out of 7 comparisons): amisulpride (RR=0.88*) and haloperidol (RR=0.64*) reducing the risk of all-cause discontinuation. While it showed inferiority to olanzapine and risperidone LAI. Clozapine and risperidone were superior over one AP (clozapine vs. haloperidol RR=0.33, risperidone vs. haloperidol RR=0.65*).

4.2.2.2.2 Pooled results with three or more RWS datasets available

There were 17 out of 25 AP comparisons which had three or more real-world studies included. We investigated whether these groups of comparisons were homogeneous or heterogeneous based on the results of their effect size estimates. A group was considered homogeneous when the majority of the individual study results from real-word studies was significantly less than 1; or greater than 1; or not different from 1.

We identified 12 AP comparisons (70.6%) with homogeneous input data: amisulpride-olanzapine, amisulpride-risperidone LAI, aripiprazole-olanzapine, aripiprazole-risperidone LAI, clozapine-haloperidol, clozapine-risperidone LAI, haloperidol-quetiapine, haloperidol-risperidone, olanzapine-quetiapine, olanzapine-risperidone, quetiapine-risperidone LAI, and risperidone LAI-risperidone.

There were 5 groups (29.4%) with heterogeneous input data: clozapine-olanzapine, clozapine-risperidone, haloperidol-olanzapine, olanzapine-risperidone LAI, and quetiapine-risperidone.

In our further analysis, we found 12 (70.6%) AP comparisons (out of the 17) which were both statistically conclusive and consistent showing relative superiority over the respective APs in the comparisons. There was one comparison (5.9%) which provided statistically conclusive but inconsistent result. As for the remaining 4 comparisons (23.5%), they were both statistically inconclusive and inconsistent.

Please note that the proportion of AP comparison with more than 3 individual studies were not different among the three categories. In particular, regarding the group with statistically conclusive and consistent findings there was 1 comparison that included 8 studies; there were 2 comparisons with 5 studies; one of them was based on 4 studies; and 8 on 3 studies. For the group with statistically conclusive but inconsistent results there was 1 comparison that relied on 5 studies. Finally, in the group of statistically inconclusive and inconsistent results there were 3 comparisons with 4 studies; one relied on 3 studies.

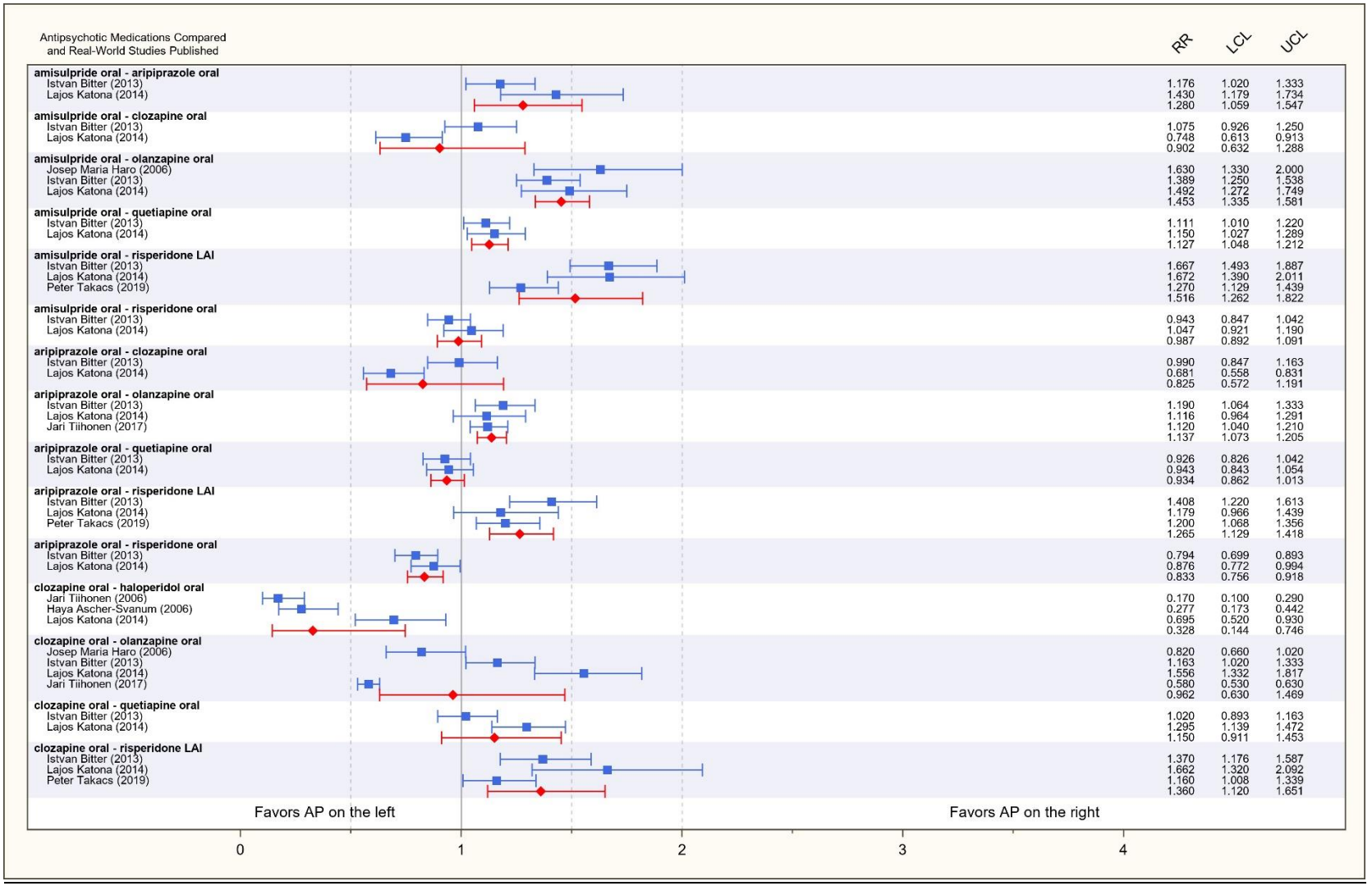

Figure 4a: Treatment discontinuation due to any reason[a]

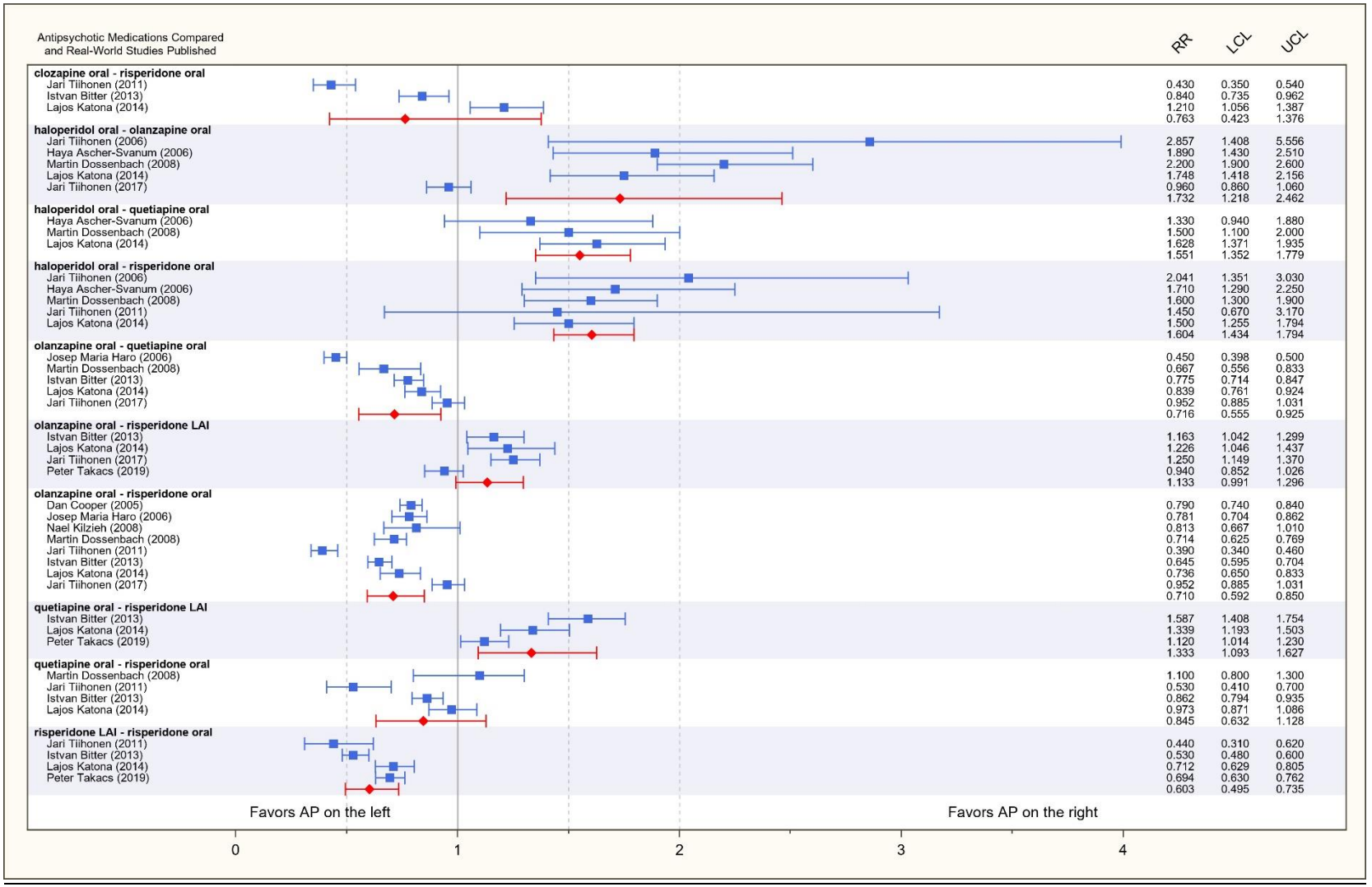

Figure 4b: Treatment discontinuation due to any reason[b]

Notes for **Figure 4a and 4b**:

[a] This is a copy of the figure published in the original paper as Figure 2: part A (Katona et al., 2021).

[b] This is a copy of the figure published in the original paper as Figure 2: part B (Katona et al., 2021).

Results of individual studies included in the meta-analysis along with pooled meta-analytic estimates based on random effect model. The figures provide the results for the 25 individual pairwise comparisons. The results of pairwise comparison are arranged in alphabetical order.

Relative Risk of discontinuation for the first and second APs is indicated as a value of <1 or >1, depending on whether the first or the second AP in the pair has superior or inferior efficacy, respectively. For example, in the clozapine vs. haloperidol pairwise comparison, clozapine was found to be superior over haloperidol as our pooled estimate was 0.33, while in the amisulpride vs. olanzapine comparison, olanzapine showed superiority over amisulpride with an RR of 1.45.

For the graphical illustration, the UCL value (5.556) was truncated at 4 in the case of the haloperidol oral–olanzapine oral pairwise comparison from the Jari Tiihonen (2006) study (Tiihonen et al., 2006).

Blue: The results of individual real-world studies; Red: Pooled estimates of current meta-analysis.

Regarding the group with both statistically conclusive and consistent outcomes the following order of superiority was found (the sign of ">" indicates superiority): olanzapine>risperidone (e.g., olanzapine was superior over risperidone), olanzapine>quetiapine, haloperidol<risperidone, risperidone LAI>risperidone, amisulpride<olanzapine, aripiprazole<olanzapine, aripiprazole<risperidone LAI, clozapine>haloperidol, amisulpride<risperidone LAI, clozapine<risperidone LAI, haloperidol<quetiapine, and quetiapine<risperidone LAI. With regard to the group with statistically conclusive but inconsistent results the order of superiority was: haloperidol<olanzapine. The remaining 4 comparisons showing statistically inconclusive and inconsistent results were: clozapine-olanzapine, quetiapine-risperidone, olanzapine-risperidone LAI, and clozapine-risperidone.

Detailed findings for each of the comparisons can be found in Online Supplementary Information (Appendix 6) in the original paper (Katona et al., 2021).

4.2.3. Previously published meta-analyses based on RCTs (RCTmeta) as compared to meta-analytic results of RWS

4.2.3.1 Selection of primary and secondary benchmarks for comparisons with RWS

Based on the result of our literature search we identified 7 meta-analyses of RCTs as suitable for benchmarks based on our criteria. One primary and, whenever available, one secondary benchmark was selected for the comparisons. Overall, for the 17 AP comparisons included in our meta-analysis with three or more input results (of the total of 25 comparisons), we were able to match the pooled results of 13 AP comparisons based on previously published meta-analyses of RCTs. For those AP comparisons where more than one meta-analysis of RCTs were available both the primary and secondary benchmarks were used.

Basic descriptive statistics about prior meta-analyses based on RCTs are provided in Table 5.

Table 5. Basic descriptive statistics of previously published meta-analyses[a]

1st Authort, Year of Publiction	Statistical Measure Calculated	AP pairs compared	Number of Trials[b]	Total Number of Patients[c]	Relative Risk	LCL of Relative Risk	UCL of Relative Risk
Beasley et al., 2007	Hazard Ratio	clozapine-olanzapine	3	409	1,20	0,90	1,60
		haloperidol-olanzapine	5	948	1,40	1,20	1,70
		olanzapine-risperidone	5	421	0,77	0,63	0,91
Soares-Weiser et al., 2013	Hazard Ratio	amisulpride-olanzapine	3	1119 (791)	1,15	0,93	1,43
		aripiprazole-olanzapine	2	1269 (566)	1,23	1,08	1,41
		clozapine-olanzapine	4	596 (477)	1,05	0,75	1,47
		haloperidol-olanzapine	5	1651 (1112)	1,54	0,93	2,56
		olanzapine-quetiapine	6	3130 (1749)	0,68	0,56	0,83
		olanzapine-risperidone	11	3482 (2117)	0,80	0,71	0,90
Samara et al., 2016	Odds Ratio	clozapine-haloperidol	3	646	0,53	0,29	1,12
		clozapine-olanzapine	7	956	1,28	0,76	2,22
		clozapine-risperidone	6	587	0,97	0,54	1,72
		haloperidol-olanzapine	5	731	1,92	1,03	4,17
		haloperidol-risperidone	2	145	0,87	0,31	2,44
		olanzapine-risperidone	2	112	0,66	0,22	2,03
Sampson et al., 2016	Risk Ratio	aripiprazole-risperidone LAI	2	723	1,20	0,77	1,89
		risperidone LAI-risperidone	2	690	1,28	0,92	1,79
Ostuzzi et al., 2017	Risk Ratio	risperidone LAI-risperidone	6	1151	1,17	0,95	1,44
Krause et al., 2018	Odds Ratio	olanzapine-risperidone	3	281	0,54	0,31	0,93
Kishimoto et al., 2019	Risk Ratio	amisulpride-olanzapine	3	796	1,07	0,91	1,27
		aripiprazole-olanzapine	8	2117	1,17	1,05	1,30
		aripiprazole-quetiapine	2	522	0,75	0,38	1,45
		clozapine-olanzapine	4	1202	1,01	0,86	1,18
		clozapine-risperidone	4	216	0,74	0,57	0,95
		olanzapine-quetiapine	8	1942	0,79	0,71	0,89
		olanzapine-risperidone	16	3131	0,88	0,83	0,93
		quetiapine-risperidone	8	3227	1,07	0,98	1,18

[a] This is a shortened version of table published in Online Supplementary Information of the original paper as eTable 3 (Katona et al., 2021).

[b] Number of randomised controlled trials included in the meta-analysis for a given comparison.

[c] The number of patients in Soares-Weiser *et. al.*, paper provides the total number of patients included in the RCTs, regardless of the target APs compared. The authors of the current investigation looked up the original papers on the RCTs included in the meta-analysis by Soares-Weiser *et. al.*, and summed up only those number of patients who were allocated to the specific target drugs compared. The originally published numbers by Soares-Weiser are displayed in the Table's cells; the numbers in the brackets are calculated by the authors.

4.2.3.2 Comparison of RWS with meta-analytic benchmarks from RCTs

The current subsection is structured based on whether RWSs yielded conclusive evidence and/or the evidence was congruent with RCTmetas. We found that the majority of the 9 RWSs (n=7; 77.8%) were congruent with RCTmetas with statistically conclusive findings. Out of the 3 RWSs with inconclusive results, 2 (66.7%) were congruent with the RCTmetas.

The results of the current study placed side by side with the results of RCTmetas are shown in a summary table (Table 6). In the next 4 sub-sections of the Results, we use this table for presentation.

4.2.3.2.1 AP comparisons of RWS with statistically conclusive ("significant") results showing congruency with RCTmetas

- olanzapine-risperidone: We found an RR of 0.71 (95% CI=0.59-0.85) favouring olanzapine. Additionally, for the primary and the secondary benchmark, we identified one RCTmeta, respectively. These meta-analyses provided statistically congruent results with our estimate (RR=0.88 (95% CI=0.83-0.93); RR=0.80 (95% CI=0.71-0.90)).
- olanzapine-quetiapine: Our meta-analysis showed an RR of 0.72 (95% CI=0.56-0.92), that favoured olanzapine. For the primary benchmark we identified one RCTmeta and we found no meta-analysis for secondary benchmark. The primary benchmark meta-analysis provided statistically congruent result with our estimate (RR=0.79 (95% CI=0.71-0.89)).
- aripiprazole-olanzapine: The pooled RR estimate was 1.14 (95% CI=1.07-1.20) which favoured olanzapine. We found one primary and no secondary RCTmeta benchmark, with the primary benchmark showing a statistically congruent result with our estimate (RR=1.17 (95% CI=1.05-1.30)).
- aripiprazole-risperidone LAI: The current meta-analysis provided an RR of 1.26 (95% CI=1.13-1.42), that favoured risperidone LAI. There was only one RCTmeta as primary benchmark, and it had a numerically congruent result with our estimate (RR=1.20 (95% CI=0.77-1.89)). The latter RCTmeta estimate, however, failed to obtain significance owing to the low number of trials included in the analysis (N=2).
- clozapine-haloperidol: Our meta-analysis provided an RR of 0.33 (95% CI=0.14-0.75), showing clozapine's advantage. For a benchmark, we found only one RCTmeta which

was numerically congruent with our pooled estimate of RR=0.53 (95% CI=0.29-1.12). The latter RCTmeta estimate did not reach statistical significance due to the low number of trials included in the analysis (N=3).

- amisulpride-olanzapine: The pooled estimate of RR was 1.45 (95% CI=1.34-1.58) which favoured olanzapine. For benchmark, we found one RCTmeta which was numerically congruent with our pooled estimate in terms of direction of RR (1.07 (95% CI=0.91-1.27)). This estimate failed to reach significance owing to the modest effect size, i.e., RR=1.07 (95% CI=0.91-1.27).
- haloperidol-olanzapine: The current meta-analysis had an RR of 1.73 (95% CI=1.22-2.46) which favoured olanzapine. Both the primary and the secondary benchmark comparison provided congruent results (RR=1.54 (95% CI=0.94-2.56); RR=1.40 (95% CI=1.20-1.70)).

4.2.3.2.2 Comparisons of RWS with statistically inconclusive results showing congruency with RCTmetas

- clozapine-olanzapine: The pooled estimate of RR was 0.96 (95% CI=0.63-1.47), yielding no significant difference. For benchmark, one RCTmeta for primary and one for secondary benchmark, respectively, were identified. These meta-analyses provided statistically congruent results with our estimate (RR=1.01 (95% CI=0.86-1.18); RR=1.05 (95%CI=0.75-1.47)), showing no difference between these two APs.
- clozapine-risperidone: Our meta-analysis provided an RR of 0.76 (95% CI=0.42-1.38) which did not reach statistical significance. For benchmark, we identified one RCTmeta, which reached a congruent result with our estimate (RR=0.74 (95% CI=0.57-0.95)).
- aripiprazole-quetiapine: The pooled RR estimate was 0.93 (95% CI=0.86-1.01), yielding no significant difference. For benchmark, we found one primary benchmark that had congruent result with our estimate (RR=0.75 (95% CI=0.38-1.45)). We note, however, that the pooled estimate of our meta-analysis was based on 2 available RWSs, instead of 3. (This estimate is not presented in Table 6 but in Figure 5).

4.2.3.2.3 Comparison of RWS with statistically conclusive results showing incongruence with RCTmetas

- haloperidol-risperidone: The pooled RR estimate of our meta-analysis was 1.60 (95% CI=1.43-1.79). For benchmark, we identified one RCTmeta which showed a

numerically incongruent result compared to our estimate (RR=0.87 (95% CI=0.31-2.44)).

- risperidone LAI-risperidone: The pooled RR estimate of our meta-analysis was 0.60 (95% CI=0.50-0.73). For benchmark, one RCTmeta for primary and one for secondary benchmark, respectively, were identified. These RCTmetas reached a numerical advantage for risperidone compared to risperidone LAI (RR=1.17 (95% CI=0.95-1.44); RR=1.28 (95% CI=0.92-1.79)), while the pooled estimate of our meta-analysis resulted in a significant superiority for risperidone LAI vs. risperidone.

4.2.3.2.4 Comparison of RWS with statistically inconclusive results showing incongruence with RCTmetas

- quetiapine-risperidone: Current meta-analysis provided an RR of 0.84 (95% CI=0.63-1.13) which did not reach statistical significance. For benchmark, one RCTmeta was found, which reached a numerically incongruent result compared to our estimate (RR=1.07 (95% CI=0.98-1.18)).

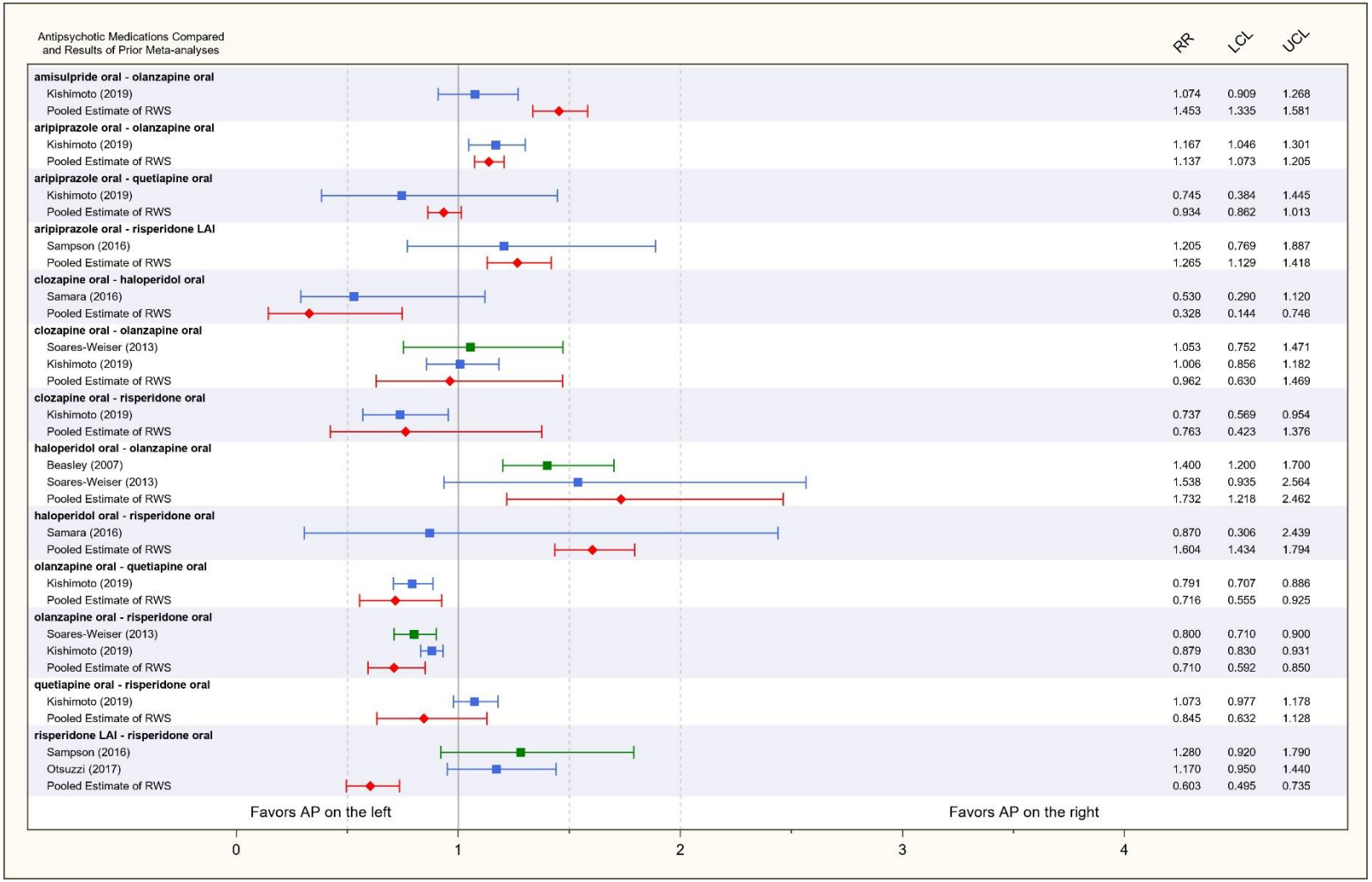

Figure 5: Effect size estimates from previously published meta-analyses of RCTs, and from current meta-analysis[a]

[a] This is a copy of the figure published in the original paper as Figure 3 (Katona et al., 2021).

Outcome measure: treatment discontinuation due to any reason

Groups: primary benchmark (blue); secondary benchmark (green); and pooled estimates of current meta-analysis (red).

Please note that for the comparison of aripiprazole-quetiapine the pooled estimate RWS is only based on two studies.

Blue: The results of individual meta-analyses based on randomised controlled trials' data considered as primary benchmark.

Green: The results of individual meta-analyses based on randomised controlled trials' data considered as secondary benchmark.

Red: Pooled estimates of current meta-analysis.

Table 6: Comparison of results from the meta-analysis of real-world studies that include three or more investigations, and from previously published meta-analyses based on RCTs[a]

Comparisons (3 or more RWS in each)[b]	Number of RWS inclu-ded	Findings conclu-sive (Yes/No)[c]	Individual study estimates are consistent (Yes/No)[d]	RR (95% CI) of our meta-analysis (based on RWS)[e]	RR (95% CI) of reference meta-analyses; Evaluation of congruency		Source of meta-analyses
					Primary benchmark	Secondary benchmark	
olanzapine-risperidone	8	Yes	Yes	0.71 (0.59-0.85)	0.88 (0.83-0.93) congruent results	0.80 (0.71-0.90) congruent results	Primary: Kishimoto Secondary: Soares-Weiser
olanzapine-quetiapine	5	Yes	Yes	0.72 (0.56-0.92)	0.79 (0.71-0.89) congruent results		Primary: Kishimoto
haloperidol-risperidone	5	Yes	Yes	1.60 (1.43-1.79)	0.87 (0.31-2.44) incongruent results		Primary: Samara
risperidone LAI-risperidone	4	Yes	Yes	0.60 (0.50-0.73)	1.17 (0.95-1.44) incongruent results	1.28 (0.92-1.79) incongruent results	Primary: Otsuzzi Secondary: Sampson
amisulpride-olanzapine	3	Yes	Yes	1.45 (1.34-1.58)	1.07 (0.91-1.27) congruent results		Primary: Kishimoto
aripiprazole-olanzapine	3	Yes	Yes	1.14 (1.07-1.20)	1.17 (1.05-1.30) congruent results		Primary: Kishimoto
aripiprazole-risperidone LAI	3	Yes	Yes	1.26 (1.13-1.42)	1.20 (0.77-1.89) congruent results		Primary: Sampson
clozapine-haloperidol	3	Yes	Yes	0.33 (0.14-0.75)	0.53 (0.29-1.12) congruent results		Primary: Samara
amisulpride-risperidone LAI	3	Yes	Yes	1.52 (1.26-1.82)			
clozapine-risperidone LAI	3	Yes	Yes	1.36 (1.12-1.65)			
haloperidol-quetiapine	3	Yes	Yes	1.55 (1.35-1.78)			
quetiapine-risperidone LAI	3	Yes	Yes	1.33 (1.09-1.63)			
haloperidol-olanzapine	5	Yes	No	1.73 (1.22-2.46)	1.54 (0.94-2.56) congruent results	1.40 (1.20-1.70) congruent results	Primary: Soares-Weiser Secondary: Beasley
clozapine-olanzapine	4	No	No	0.96 (0.63-1.47)	1.01 (0.86-1.18) congruent results	1.05 (0.75-1.47) congruent results	Primary: Kishimoto Secondary: Soares-Weiser
quetiapine-risperidone	4	No	No	0.84 (0.63-1.13)	1.07 (0.98-1.18) incongruent results		Primary: Kishimoto
olanzapine-risperidone LAI	4	No	No	1.13 (0.99-1.30)			
clozapine-risperidone	3	No	No	0.76 (0.42-1.38)	0.74 (0.57-0.95) congruent results		Primary: Kishimoto

[a] This is a copy of the table published in the original paper as Table 2 (Katona et al., 2021).

[b] APs underlined indicates superiority over their pairs compared to.

[c] It indicates statistically significant difference between the two APs (13/17 AP pairs).

[d] Point in the same direction.

[e] We identified 12 out of 17 comparisons with both RWS and RCT meta-analyses available.

4.2.3.2.5 No RCTmetas were available

No RCTmetas could be identified for 5 comparisons, including amisulpride-risperidone LAI; clozapine-risperidone LAI; haloperidol-quetiapine; quetiapine-risperidone LAI; and olanzapine-risperidone LAI.

5. Discussion

5.1 Discussion of the results of first study

The first study addressed the question whether the application of antipsychotic polypharmacy has advantages over monotherapy in the treatment of subjects with schizophrenia or schizoaffective disorders. The clinical importance of this question is highlighted by the fact that despite major treatment efforts for a substantial proportion of patients the symptoms cannot fully be controlled by APs (c.f., treatment resistant schizophrenia). Subjects often end up with frequent and/or prolonged hospitalisation, poor quality of life and an increased and premature mortality. The general recommendation of leading guidelines is to use one of the antipsychotic medications in monotherapy for the treatment of schizophrenia and other psychotic disorders (Freedman et al., 2005; Keepers et al., 2020; Lehman et al., 2004; Leucht et al., 2013; NICE Guideline CG178, 2014). Notwithstanding this recommendation, the use of antipsychotics in combination (polypharmacy) is widely applied in clinical practice (Ballon & Stroup, 2013; Barnes & Paton, 2011; Faries et al., 2005; Gallego et al., 2012; Gamón et al., 2021; Honer et al., 2007; Kasteridis et al., 2019). However, evidence of the effectiveness of this strategy against monotherapy is scarce (Ascher-Svanum et al., 2012; Correll et al., 2009; Essock et al., 2011; Fleischhacker & Uchida, 2014; Galling et al., 2017; Josiassen et al., 2005; Rosenheck et al., 2009; Rupnow et al., 2007; Tiihonen et al., 2019), even though the guidelines typically recommend the use of polypharmacy as a last resort (Foster & King, 2020; Lähteenvuo & Tiihonen, 2021).

To answer our study question, the use of clinical trials would not be sufficient as many such trials would be needed to perform a series of head-to-head comparisons of treatment strategies (monotherapy vs. polypharmacy) using multiple APs. In order to obtain a robust evidence, in the first study which was based on the analysis of databases of the National Health Insurance Fund Administration of Hungary, we included 14 AP medications involving more than 13 thousand subjects. In terms of time to all-cause treatment discontinuation, the findings of the first study indicate that switching to SGA monotherapy in the overwhelming majority of comparisons provides an advantage over polypharmacy, with the exception of clozapine, which is mainly used in lower daily doses in Hungary. (I think that the data on clozapine would need a further specifically focused study to understand the specifics of its clinical use in Hungary). As for the oral

formulations of FGAs, the results showed that there was no advantage of monotherapy over polypharmacy; while for depot formulations of FGAs an advantage for polypharmacy was detected regarding time to all-cause discontinuation. With regard to mortality and psychiatric hospitalisation rates, we found a statistically significant advantage of polypharmacy over monotherapy.

Overall, the principal findings of the first study indicated that (1) monotherapy is superior when the endpoint was all-cause treatment discontinuation, while (2) polypharmacy showed superiority when the endpoints were psychiatric hospitalisation and mortality due to any reason. As revealed in our first study *"…while mortality and hospitalization represent important specific clinical endpoints for effectiveness, time elapsing to all-cause discontinuation provides a key pragmatic measure for the clinicians."* (Katona et al., 2014, p. 253)

In the light of the findings of our first study, we concluded that the use of appropriate, and multiple, endpoints are essential for a comprehensive evaluation of the various treatments. All-cause treatment discontinuation might be the gold standard of endpoints used in RWSs targeting the treatment of schizophrenia with antipsychotics as it captures the length of therapies, which is key in the treatment of schizophrenia, regardless of the reasons why the medications are discontinued. Nonetheless, to investigate the reasons why there are (or are no) differences between APs and/or treatment strategies (e.g., monotherapy vs. polypharmacy) in addition to using all-cause treatment discontinuation as measurement, it is important to identify further endpoints which might reveal important factors that both clinicians and subjects can benefit from. This is consistent with our general conclusion that the comparison of medications via multiple endpoints is essential. Taking our first study as an example, it is not sufficient to measure only soft endpoints (e.g., all-cause treatment discontinuation), but it is also important to investigate hard endpoints (such as [psychiatric] hospitalisation and mortality) to provide strong evidence for their effectiveness.

Our first study has a number of limitations, including the fact that we focused on therapy changers, i.e., on patients who switched from an initial AP medication to a new one (MA group) or received a second AP to the existing one (PA group). Combinations with more than two APs were not investigated due to their low prevalence, which restricts generalisability. An additional limitation is the fact that patients may be subjected to

monotherapy or polypharmacy strategies based on clinical or demographic characteristics and prior disease history. In our investigation, however, we conducted propensity score adjusted analyses which indicated that the results remain essentially unchanged even after matching for baseline characteristics. In addition, the allocation of patients into the two study arms might have been influenced by prescribers' preference for monotherapy or polypharmacy. However, we found no difference between MA and PA in the ratio of polypharmacy vs. monotherapy applied by psychiatrists who contributed prescriptions for patients in this study. Moreover, although the principal analysis focused on schizophrenia or schizoaffective disorder in subsidiary analyses, we found indication that our findings are applicable for the core diagnosis of schizophrenia. Finally, since our study relied on a database analysis of deidentified records, which include diagnoses given by the physicians who prescribed the medications, we could not further validate the records.

5.2 Discussion of the results of second study

The majority of RWSs was focusing on the comparison of AP medications that had already been available on the market for many years. We thought that sufficient empirical evidence has been gathered, making possible to summarise and analyse the results of observational studies, including the ones based on database analyses, which had been accumulating over 2-3 decades.

In our second study, which included a meta-analysis of RWSs targeting the pharmacological treatment of schizophrenia, we compared 8 antipsychotic medications measuring effectiveness by using all-cause treatment discontinuation as an endpoint. Based on the results of this study, we can conclude that for most comparisons with three or more RWSs, our results indicated that the real-world studies led to statistically conclusive and even more importantly, consistent findings throughout the individual investigations. In fact, of the 17 studies that provided sufficient empirical data (i.e., ≥3 RWS), both conclusive and consistent results occurred for 70.6% (12 of 17) of the studies. With regard to those comparisons which did not meet the criteria for yielding both conclusive and consistent pooled results in our second study, the picture may vary in terms of the reasons of why they did not. I think that the factors that might come into play can be the lack of difference between AP medications in real-life settings, variation in study samples, heterogeneity of study populations, cohort effects, differing study designs, or differences in clinical practices of how AP medications are used in various countries.

Specifically, there were two comparisons (haloperidol oral vs. olanzapine oral with 5 studies, and olanzapine oral vs. risperidone LAI with 4 studies; one with conclusive and the other one with numerically supportive results, respectively), which each included one study with different directions compared to the rest. For one other comparison (quetiapine vs. risperidone with 4 studies), the result was inconclusive and inconsistent, which might be attributable to the similarity in effectiveness using all-cause treatment discontinuation. Finally, there were two comparisons (clozapine vs. olanzapine with 4 studies, and clozapine vs. risperidone with 3 studies) with pooled results which were inconclusive due to the wide variation of efficacy estimates from RWSs.

Considering the results of our second study, regionally specific prescribing practice may explain the relative lack of effectiveness of clozapine in the Hungarian population where clozapine is typically applied in lower doses (Bitter et al., 2013; Katona et al., 2014). Inconsistent RR estimate within the same country may also be explained by cohort effects, for example, the introduction of new LAIs in the Hungarian market (Takács et al., 2019).

In the second study we also examined whether the pooled results of our meta-analysis are consistent with the pooled results of randomised controlled trials. (Please note that the previously published meta-analyses based on clinical trials predominantly focused on the drop-out data, while the results of RWSs in our meta-analysis were about all-cause treatment discontinuation.) Since the majority of RCTs used placebo as comparator, we could not identify pooled results of meta-analyses based on RCTs for some of the comparisons we had in the RWD analyses. While head-to-head comparisons were more common in real-world investigations, they were significantly less common in randomised controlled trials, as expected. We found that data from RCT meta-analyses were only accessible for 12 of 17 RWS comparisons with adequate evidence (i.e., three or more real-world studies included); these comprised the set of pairwise comparisons for the evaluation of the congruency between RWS and RCT research.

The results of our second study indicate that there was a good congruency between the results of the real-world studies and the randomised controlled trials (75%; i.e., nine of 12 comparisons where both real-world and RCT results were available).

Based on the principal finding of our second study, discussed above, it can be concluded that randomised controlled trials, in spite of their limitations, deliver evidence that is

generalisable to real-world settings. It is important to note that this conclusion does not imply that all the results that came from randomised controlled trials can be generalisable to real-world settings. Although the results of RCTs showed a good congruency with real-world studies based on large healthcare datasets, the predictive value of randomised controlled trials for clinical practice should be assessed on a regular basis. In particular, the need arises for the investigation of the generalisability of the RCT results in long-term multi-arm naturalistic studies or in analyses of healthcare databases. Moreover, due to the good congruency between the results of RCTs and RWSs, not only can the above inference be drawn but we can also conclude that real-world studies might be able to provide guidance for situations where evidence is not available from randomised controlled trials. It is to be noted that our first study provided the relevant empirical support for this conclusion.

Based on the findings of the second study, we concluded that the pooled results of RCTs trials and RWSs were similar for many antipsychotics. Despite the high degree of agreement, however, the question arises as to whether it is justifiable to compare the pooled results of RCTs and RWSs, which, respectively, were based on completely different approaches of study design and analyses. To address this issue, we considered the following question: What are the potential factors that should be considered in order to answer the question, i.e., in what way do clinical trials and RWSs differ the most? These factors are briefly discussed below.

(1) Clinical trials use the random assignment, while RWSs do not. In clinical trials, subjects are randomised to one of the treatment arms including placebo. In RWSs, the patient's demographics, medical history, specific clinical conditions, and other considerations determine which treatment arms subjects are assigned to. If only random vs. non-random classification is considered, and all-cause treatment discontinuation/drop out is the endpoint, it can be expected that in case of two subjects with the same background characteristics, the one without random assignment might keep taking the medication longer as compared to the other one who was randomly assigned to.

(2) With respect to subject characteristics, RCTs have quite homogeneous treatment groups (only those subjects can qualify for the trial who have no or only a few predefined comorbidities, are not elderly, are neither violent nor hostile, etc.), and these groups are similar to each other. RWSs have heterogeneous treatment groups, and the characteristics

of subjects in different treatment arms are not necessarily similar. Based on these aspects it can be expected that subjects in RCTs might have better adherence to their medications (Kishimoto et al., 2014).

Taken together, there might be potential differences between RCTs and RWSs measuring all-cause treatment discontinuation, but we think that overall, the above discussed effects are expected to balance each other out.

Based on the empirical results from the second study, it is important to reiterate the question whether randomised controlled trials and RWSs complement each other. In order to answer this question in this subsection, we discuss the relevant features of RCTs and RWSs so that we can identify the respective features of two approaches, thereby making possible the comparisons.

With respect to RCTs, it is essential to highlight that before a new medication is available for the intended target population, it is mandatory to investigate if a drug is efficient, and to make sure that it does not cause a harm (as judged in a risk-benefit context). To gain enough evidence with regard to these issues, it is universally accepted that randomised controlled trials during clinical development are essential to support the decision making on whether a drug can be used in clinical practice.

To test if a medication is beneficial in treating a particular disorder, it is crucial to adopt the most appropriate endpoint for use in clinical trials. As for the primary endpoints, the focus is usually on examining the effect of a new medication compared to placebo, or to an active comparator, by applying one of the psychopathological rating scales (for example PANSS). To make sure that only the effect of the therapeutic interventions (including placebo) is measured, it is critical to guarantee that the subject population across the various therapeutic arms is homogeneous, e.g., subjects have very similar demographic and clinical characteristics in both the investigational and control arms. In addition to measuring efficacy, the safety of the new medication is also closely monitored in clinical trials as mentioned above, by collecting information on adverse events. Furthermore, the number of subjects who dropped out and the reasons of those drop-outs need to be recorded in each clinical trial. The decision on approval for marketing can be made by the competent authorities, once a series of clinical trials have been conducted and the final analyses have been completed – usually on pooled data of multiple clinical trials. In clinical trials targeting the pharmacological treatment of schizophrenia,

regulatory agencies require only "*statistically significant between-treatment difference*" (Katz, 2004, p. 314) against a comparator. In most cases in regulatory studies, the comparator represents placebo since as stated "*the placebo-controlled trial is the most efficient trial design, i.e., for an effective treatment, the likelihood that a difference will be seen between treatment and control is greatest with a placebo (inactive) treatment than with any other potentially active treatment"* (Katz, 2004, p. 312). Furthermore, *"for treatments of neurologic and psychiatric disease, there are no predetermined treatment effect sizes established."* (Katz, 2004, p. 314) For most of the currently approved APs two or three confirmatory pivotal trials were endorsed to support the claim of efficacy.

In contrast, RWSs are usually conducted once the new medication has been approved by regulatory agencies. These studies do not explicitly focus on demonstrating a particular effect as the evidence is already available, but rather on the overall effectiveness of medications. They usually investigate if a new drug is more effective, compared to other drugs that are approved for marketing. To demonstrate effectiveness, in most cases a clinically more directly relevant practical endpoint is used (as compared to the endpoints that clinical trials apply), e.g., all-cause treatment discontinuation, detailed data on the emergence and subsequent follow-up of side effects, rate of hospitalisation or mortality. Furthermore, considering that observational studies have large sample size, it is also important to collect as much information as possible about the side effects of a medication newly placed on the market.

Thus, answering the question of whether RCTs and RWSs complement each other, we conclude that they need to co-exist, complementing each other as RCTs play crucial role in the early phase of drug development, while RWSs do their duties in late phase development, or even more after the launch of a medication. As discussed, clinical trials mainly focus on efficacy and safety, therefore right after the regulatory approval what we know is that a new medication is available in the market with proven efficacy compared mainly to a comparator (often to placebo only), and with proven safety in terms of causing significant side effects, assessed in a risk benefit context. On the other hand, RWSs measure effectiveness comparing multiple medications, and, depending on the aim of the study, may capture important safety information as well.

In the context of the above discussed considerations, it is important to highlight that our second study revealed that in the majority of the pairwise comparisons both RCTs and

RWSs draw similar conclusions (i.e., were highly congruent) with respect to which antipsychotic medication has better performance.

A potential limitation of our second investigation of RWS and RCT meta-analyses could be that the studies included into the two analyses may have relied on different patient cohorts since therapeutic guidelines and practices changed over time with the introduction of newly approved APs to the market. However, an overview of publication dates and entry time window (2005 to 2019) for the two types of studies (i.e., RWS and RCT meta-analyses) reveals that they covered similar time periods. In addition, the inconsistent findings in RCTs versus RWSs, that we found, about the comparative effectiveness of oral versus LAI formulations of second-generation APs have been the focus of discussion in the literature: *"LAIs are thought to be better via improved adherence, not via intrinsically better efficacy. Therefore, it is unclear whether LAIs were not superior because compliance with OAPs was good enough in the context of RCTs."* (Kishimoto et al., 2014, p. 209). Furthermore, our findings from the real-world studies that rely mostly on a limited set of countries (e.g., Scandinavian countries and Hungary) can be influenced by regional differences (Bitter et al., 2008), thus we cannot be certain that the results would generalise to most countries and regions of the world. Potentially important regional characteristics of the use of APs include, for example, the lower rate of using LAIs in the USA, a geographical region where large scale studies are conducted. We note, however, that some of RWSs cover broad geographical regions that include the four continents or multiple European countries, which can add support to the notion of the broader generalisability of the results.

5.3 General discussion

Information from RCTs helps physicians and other participants of the health care system for choosing the best treatment for the patients, according to the societal needs. The decision making process, however, cannot necessarily be optimised based on only RCTs for multiple reasons (see Introduction 1.3). Moreover, the overwhelming majority of RCTs is built on study designs that provide a limited diversity for treatment comparisons (Ioannidis, 2009). For example, comparator bias can be typical in RCTs, e.g., it can occur when a new treatment is compared with another treatment which was introduced to the market very long time ago (i.e., chlorpromazine or haloperidol) or when a sponsor wants to facilitate the trial success, i.e., the superiority (or in some cases non-inferiority) of the

new medication by selecting a less efficacious comparator. Regulatory bias is another example which is resulted from the recommendation of the use of placebo as a primary comparator in a given study (Ioannidis, 2009). Last, but not least, the target population can be rather limited by selecting the 'best patient' or even the 'professional patient' for the RCTs (Kishimoto et al., 2014).

The studies included in my dissertation addressed this limited diversity of data coming from RCTs in two concrete situations. First, by focusing on polypharmacy vs. monotherapy comparisons, we compared treatment strategies which are typically not investigated in the antipsychotic development for the approval of a single drug (as they are not applied in combination at this development and regulatory stage). Second, we compared the whole set of AP monotherapies applied in clinical practice based on real-world data. In order to achieve this aim, we conducted the first comprehensive meta-analysis of data obtained from real-world studies.

To validate whether our approaches can sufficiently address the problem of limited diversity of data coming from RCTs, we investigated the congruency between RWD and RCT findings. Specifically, in our second study, we performed a multiple treatment meta-analysis encompassing results from non-randomised studies, and assessed the consistency of the input data, investigating potential biases. To examine the potential gap/discrepancies between RWSs and RCTs, first, we selected the results of previously published meta-analyses based on RCTs, and then investigated whether the AP comparisons are congruent or incongruent with each other.

Specifically, for the purpose of our validation efforts we defined, to the best of our knowledge for the first time in the literature, an operationalised benchmark index which we termed congruency. On the basis of this benchmark index, we were able to demonstrate that the overwhelming majority of AP comparisons had a good congruency across different types of trials (i.e., RWD vs. RCT). We think that for decision makers (e.g., various health agencies and/or health insurance companies) it would be important to adopt such an approach and methodology to assess the comparative effectiveness of treatments on an ongoing basis, thereby making the decision adaptive to the most up to date information. We considered the approach useful for synthetising evidence for guidelines and decision making, but we think they could be further operationalised based on additional investigations. One important step forward would be the adoption of

common effect size measure since various studies and meta-analyses tend to use a number of different measurements such as odds ratio (OR), relative risk (RR), hazard ratio (HR), risk difference (RD), incidence rate ratio (IRR). Fusar-Poli and Radua (2018) recommended that all of these measurements should be converted into OR before conducting an evidence synthesis (Fusar-Poli & Radua, 2018).

With respect to a common effect size measure it is important to highlight that, in those clinical trials, especially Phase 3 trials, which have long study duration (at least one year) and follow-up period (e.g., an additional year) multiple relevant endpoints could be measured, including, for example, all-cause treatment discontinuation, "clinical worsening", disease exacerbation, remission, disease free survival, progression free survival, overall survival, patient reported outcomes. As pointed out in our second study: *"The adoption of all-cause treatment discontinuation as one of the endpoints in future RCTs may help better translate and back-translate treatment data between clinical trials and clinical practice."* (Katona et al., 2021, p. 1384)

To make this approach feasible in practice, I think that similar to the coding of adverse events, a coding system for treatment discontinuation needs to be developed since the current clinical trial practice classifies discontinuation events in an ad-hoc/naïve fashion, varying from trial to trial (e.g., discontinuation due to efficacy, or safety, or to administrative reasons). Formalisation of the set of criteria would be an important future step since it would make possible more efficient combined analyses of real-world clinical trial events at the stage of regulatory submission and at the evaluation for approval.

6. Conclusions

6.1 Conclusions of first study

The principal finding of our first study that polypharmacy (the parallel use of two antipsychotic medications) shows an advantage in mortality and psychiatric hospitalisations can be interpreted as an indication that combination treatments may be more efficacious during exacerbations of psychotic symptoms, which can lead to hospitalisations or death, while monotherapy is superior over polypharmacy for long-term sustained treatment. Specifically, in terms of time to all-cause treatment discontinuation, our findings indicate that switching to SGA monotherapy (particularly with amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, and risperidone LAI) in the overwhelming majority of cases provides an advantage over polypharmacy with the exception of clozapine which shows no difference between the two strategies. As to the oral formulations of FGAs, the results showed that there was no advantage of monotherapy over polypharmacy; while for LAI formulations of FGAs there was an advantage for polypharmacy detected, regarding time to all-cause discontinuation.

Our study also highlights that the head-to-head comparison of medications should be conducted on the basis of multiple endpoints, by making sure that the final inferences are drawn carefully, taking into consideration all relevant aspects of the medication effects. Overall, our results highlight the significance of examining multiple secondary endpoints in long-term studies of schizophrenia, since a single composite measure such as all-cause treatment discontinuation may not be able to distinguish specific differences in major clinically relevant events including hospitalisation or mortality. Nonetheless, despite the fact that hospitalisation and death are significant individual clinical endpoints, time elapsing to all-cause treatment discontinuation offers a very practical metric for doctors.

Thus, our study, similar to some of the former studies, underlines the importance of the use of real-world data to provide evidence on those scientific questions which cannot sufficiently be addressed via randomised controlled trials.

6.2 Conclusions of second study

The principal conclusion of our second study is that there is a good congruency between the results of randomised controlled trials and real-world studies (investigating antipsychotic medications for subjects suffering from schizophrenia) based on time to all-cause treatment discontinuation. In addition, the results of our meta-analysis highlight that there is a good consistency between the results coming from individual real-world studies.

Taking together all the results of our study, there is a promise that the findings of the real-world studies would provide evidence for clinicians for everyday clinical practice. Importantly, real-world studies data, pertaining to comparisons of antipsychotic medications that have not yet been exposed to clinical testing in randomised controlled trials, are critical for three main reasons. First, they may give a provisional direction to practicing doctors in instances when no data from randomised controlled trials are available. Second, they can offer precise testable hypotheses for clinically significant unresolved questions in future clinical studies. Third, real-world studies analysis results can give critical information to regulators on design needs for future research.

Although randomised controlled trials have been considered as gold standard in clinical development for providing evidence for efficacy and safety of newly developed medications, real-world data have increasingly been playing an important role, for example, in measuring and comparing how effective the medications are in real life.

7. Summary

To control symptoms of patients with schizophrenia, the use of antipsychotic monotherapy is recommended. The application of antipsychotics in combination (polypharmacy), however, is common in clinical practice. To investigate the gap between theory and real-life clinical practice, in the first investigation we conducted a nationwide population-based effectiveness study. The primary endpoint was time to all-cause treatment discontinuation, while the secondary endpoints were psychiatric hospitalisation and mortality. Time to all-cause discontinuation indicated superiority for switching to monotherapy over polypharmacy for the majority of oral and long-acting injectable (LAI) second-generation antipsychotics. As to the oral formulations of first-generation antipsychotics, there was no difference between monotherapy and polypharmacy, while LAI formulations had an advantage for polypharmacy. Polypharmacy was associated with a lower likelihood of psychiatric hospitalisation and mortality. Our finding that monotherapy is superior to polypharmacy *"…for long-term sustained treatment whereas polypharmacy has advantage in mortality and psychiatric hospitalizations suggests that combination treatments may be more efficacious during exacerbation of psychotic symptoms."* (Katona et al., 2014, p. 253)

Although randomised controlled trials (RCTs) play a crucial role in clinical drug development, the generalisability of their findings has been questioned. To overcome this issue, an increasing number of observational studies and real-world database analyses have been conducted. To investigate how congruent the results of RCTs and real-world studies (RWSs) are, in the second study, we conducted a meta-analysis of data obtained from real-world settings; then, we compared the results of this meta-analysis with the previously published RCT meta-analyses. We focused on studies which targeted the antipsychotic treatment of schizophrenia. Our meta-analysis indicated that the real-world studies yielded statistically conclusive and, clinically even more importantly, consistent findings across the individual investigations. The main finding was that for the overwhelming majority of comparisons there was a good congruency between RWS and RCT results. Thus, RCTs can provide evidence which is generalisable to real-world settings. Moreover, RWSs can provide guidance for situations where no evidence is available from RCTs. We consider this as an important finding not only for clinicians and researchers but also for regulators.

8. References

Ascher-Svanum, H., Zhu, B., Faries, D., Landbloom, R., Swartz, M., & Swanson, J. (2006). Time to discontinuation of atypical versus typical antipsychotics in the naturalistic treatment of schizophrenia. BMC psychiatry, 6, 8. https://doi.org/10.1186/1471-244X-6-8

Ascher-Svanum, H., Brnabic, A. J., Lawson, A. H., Kinon, B. J., Stauffer, V. L., Feldman, P. D., & Kelin, K. (2012). Comparison of patients undergoing switching versus augmentation of antipsychotic medications during treatment for schizophrenia. Neuropsychiatric disease and treatment, 8, 113–118. https://doi.org/10.2147/NDT.S30268

Ballon, J., & Stroup, T. S. (2013). Polypharmacy for schizophrenia. Current opinion in psychiatry, 26(2), 208–213. https://doi.org/10.1097/YCO.0b013e32835d9efb

Barnes, T. R., & Paton, C. (2011). Antipsychotic polypharmacy in schizophrenia: benefits and risks. CNS drugs, 25(5), 383–399. https://doi.org/10.2165/11587810-000000000-00000

Beasley, C. M., Jr, Stauffer, V. L., Liu-Seifert, H., Taylor, C. C., Dunayevich, E., & Davis, J. M. (2007). All-cause treatment discontinuation in schizophrenia during treatment with olanzapine relative to other antipsychotics: an integrated analysis. Journal of clinical psychopharmacology, 27(3), 252–258. https://doi.org/10.1097/JCP.0b013e3180582426

Bell, M., Milstein, R., Beam-Goulet, J., Lysaker, P., & Cicchetti, D. (1992). The Positive and Negative Syndrome Scale and the Brief Psychiatric Rating Scale. Reliability, comparability, and predictive validity. The Journal of nervous and mental disease, 180(11), 723–728. https://doi.org/10.1097/00005053-199211000-00007

Bermanzohn, P. C., Porto, L., Arlow, P. B., Pollack, S., Stronger, R., & Siris, S. G. (2000). Hierarchical diagnosis in chronic schizophrenia: a clinical study of co-occurring syndromes. Schizophrenia bulletin, 26(3), 517–525. https://doi.org/10.1093/oxfordjournals.schbul.a033472

Bitter, I., Czobor, P., Borsi, A., Fehér, L., Nagy, B. Z., Bacskai, M., Rakonczai, P., Hegyi, R., Németh, T., Varga, P., Gimesi-Országh, J., Fadgyas-Freyler, P., Sermon, J., & Takács, P. (2017). Mortality and the relationship of somatic comorbidities to mortality in schizophrenia. A nationwide matched-cohort study. European psychiatry : the journal of

the Association of European Psychiatrists, 45, 97–103. https://doi.org/10.1016/j.eurpsy.2017.05.022

Bitter, I., Katona, L., Zámbori, J., Takács, P., Fehér, L., Diels, J., Bacskai, M., Lang, Z., Gyáni, G., & Czobor, P. (2013). Comparative effectiveness of depot and oral second generation antipsychotic drugs in schizophrenia: a nationwide study in Hungary. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology, 23(11), 1383–1390. https://doi.org/10.1016/j.euroneuro.2013.02.003

Bitter, I., Treuer, T., Dyachkova, Y., Martenyi, F., McBride, M., & Ungvari, G. S. (2008). Antipsychotic prescription patterns in outpatient settings: 24-month results from the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology, 18(3), 170–180. https://doi.org/10.1016/j.euroneuro.2007.08.001

Blair, H. A. (2022) Paliperidone palmitate intramuscular 6-monthly formulation in schizophrenia: a profile of its use. Drugs Ther Perspect 38, 335–342. https://doi.org/10.1007/s40267-022-00931-9

Buckley, P. F., Miller, B. J., Lehrer, D. S., & Castle, D. J. (2009). Psychiatric comorbidities and schizophrenia. Schizophrenia bulletin, 35(2), 383–402. https://doi.org/10.1093/schbul/sbn135

Bull J. P. (1959). The historical development of clinical therapeutic trials. Journal of chronic diseases, 10, 218–248. https://doi.org/10.1016/0021-9681(59)90004-9

Cooper, D., Moisan, J., Gaudet, M., Abdous, B., & Grégoire, J. P. (2005). Ambulatory use of olanzapine and risperidone: a population-based study on persistence and the use of concomitant therapy in the treatment of schizophrenia. Canadian journal of psychiatry. Revue canadienne de psychiatrie, 50(14), 901–908. https://doi.org/10.1177/070674370505001404

Correll, C. U., Rummel-Kluge, C., Corves, C., Kane, J. M., & Leucht, S. (2009). Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. Schizophrenia bulletin, 35(2), 443–457. https://doi.org/10.1093/schbul/sbn018

Correll, C. U., Solmi, M., Croatto, G., Schneider, L. K., Rohani-Montez, S. C., Fairley, L., Smith, N., Bitter, I., Gorwood, P., Taipale, H., & Tiihonen, J. (2022). Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. World psychiatry : official journal of the World Psychiatric Association (WPA), 21(2), 248–271. https://doi.org/10.1002/wps.20994

Cox, D. R. (1972). Regression Models and Life-Tables. Journal of the Royal Statistical Society. Series B (Methodological), 34(2), 187–220. Retrieved 2022. November 10. from http://www.jstor.org/stable/2985181

Czobor, P., & Bitter, I. (2022) Pharmacologic treatment of negative symptoms: focus on efficacy. In Managing Negative Symptoms of Schizophrenia, Bitter, I. (eds.) Oxford University Press (pp. 67-86.) Retrieved 2023. February 3. from https://doi.org/10.1093/med/9780198840121.001.0001

Dagenais, S., Russo, L., Madsen, A., Webster, J., & Becnel, L. (2022). Use of Real-World Evidence to Drive Drug Development Strategy and Inform Clinical Trial Design. Clinical pharmacology and therapeutics, 111(1), 77–89. https://doi.org/10.1002/cpt.2480

DE Hert, M., Cohen, D., Bobes, J., Cetkovich-Bakmas, M., Leucht, S., Ndetei, D. M., Newcomer, J. W., Uwakwe, R., Asai, I., Möller, H. J., Gautam, S., Detraux, J., & Correll, C. U. (2011a). Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World psychiatry: official journal of the World Psychiatric Association (WPA), 10(2), 138–151. https://doi.org/10.1002/j.2051-5545.2011.tb00036.x

DE Hert, M., Correll, C. U., Bobes, J., Cetkovich-Bakmas, M., Cohen, D., Asai, I., Detraux, J., Gautam, S., Möller, H. J., Ndetei, D. M., Newcomer, J. W., Uwakwe, R., & Leucht, S. (2011b). Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World psychiatry: official journal of the World Psychiatric Association (WPA), 10(1), 52–77. https://doi.org/10.1002/j.2051-5545.2011.tb00014.x

Demjaha, A., Lappin, J. M., Stahl, D., Patel, M. X., MacCabe, J. H., Howes, O. D., Heslin, M., Reininghaus, U. A., Donoghue, K., Lomas, B., Charalambides, M., Onyejiaka, A., Fearon, P., Jones, P., Doody, G., Morgan, C., Dazzan, P., & Murray, R. M. (2017). Antipsychotic treatment resistance in first-episode psychosis: prevalence, subtypes and

predictors. Psychological medicine, 47(11), 1981–1989. https://doi.org/10.1017/S0033291717000435

Dossenbach, M., Pecenak, J., Szulc, A., Irimia, V., Anders, M., Logozar-Perkovic, D., Peciukaitiene, D., Kotler, M., Smulevich, A. B., West, T. M., Lowry, A. J., & Treuer, T. (2008). Long-term antipsychotic monotherapy for schizophrenia: disease burden and comparative outcomes for patients treated with olanzapine, quetiapine, risperidone, or haloperidol monotherapy in a pan-continental observational study. The Journal of clinical psychiatry, 69(12), 1901–1915.

Eack, S. M., & Newhill, C. E. (2007). Psychiatric symptoms and quality of life in schizophrenia: a meta-analysis. Schizophrenia bulletin, 33(5), 1225–1237. https://doi.org/10.1093/schbul/sbl071

Essock, S. M., Schooler, N. R., Stroup, T. S., McEvoy, J. P., Rojas, I., Jackson, C., Covell, N. H., & Schizophrenia Trials Network (2011). Effectiveness of switching from antipsychotic polypharmacy to monotherapy. The American journal of psychiatry, 168(7), 702–708. https://doi.org/10.1176/appi.ajp.2011.10060908

Faries, D., Ascher-Svanum, H., Zhu, B., Correll, C., & Kane, J. (2005). Antipsychotic monotherapy and polypharmacy in the naturalistic treatment of schizophrenia with atypical antipsychotics. BMC psychiatry, 5, 26. https://doi.org/10.1186/1471-244X-5-26

Fleischhacker, W. W., Hummer, M., Kurz, M., Kurzthaler, I., Lieberman, J. A., Pollack, S., Safferman, A. Z., & Kane, J. M. (1994). Clozapine dose in the United States and Europe: implications for therapeutic and adverse effects. The Journal of clinical psychiatry, 55 Suppl B, 78–81.

Fleischhacker, W. W., & Uchida, H. (2014). Critical review of antipsychotic polypharmacy in the treatment of schizophrenia. The international journal of neuropsychopharmacology, 17(7), 1083–1093. https://doi.org/10.1017/S1461145712000399

Foster, A., & King, J. (2020). Antipsychotic Polypharmacy. Focus (American Psychiatric Publishing), 18(4), 375–385. https://doi.org/10.1176/appi.focus.20190047

Freedman R. (2005). The choice of antipsychotic drugs for schizophrenia. The New England journal of medicine, 353(12), 1286–1288. https://doi.org/10.1056/NEJMe058200

Fusar-Poli, P., & Radua, J. (2018). Ten simple rules for conducting umbrella reviews. Evidence-based mental health, 21(3), 95–100. https://doi.org/10.1136/ebmental-2018-300014

Gallego, J. A., Bonetti, J., Zhang, J., Kane, J. M., & Correll, C. U. (2012). Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophrenia research, 138(1), 18–28. https://doi.org/10.1016/j.schres.2012.03.018

Galling, B., Roldán, A., Hagi, K., Rietschel, L., Walyzada, F., Zheng, W., Cao, X. L., Xiang, Y. T., Zink, M., Kane, J. M., Nielsen, J., Leucht, S., & Correll, C. U. (2017). Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. World psychiatry : official journal of the World Psychiatric Association (WPA), 16(1), 77–89. https://doi.org/10.1002/wps.20387

Gamón, V., Hurtado, I., Salazar-Fraile, J., & Sanfélix-Gimeno, G. (2021). Treatment patterns and appropriateness of antipsychotic prescriptions in patients with schizophrenia. Scientific reports, 11(1), 13509. https://doi.org/10.1038/s41598-021-92731-w

Guy, W. (1976). Clinical Global Impressions, ECDEU Assessment Manual for Psychopharmacology, revised (DHEW Publ. No. ADM 76-338). National Institute of Mental Health. 218-222.

Haro, J. M., Kamath, S. A., Ochoa, S., Novick, D., Rele, K., Fargas, A., Rodríguez, M. J., Rele, R., Orta, J., Kharbeng, A., Araya, S., Gervin, M., Alonso, J., Mavreas, V., Lavrentzou, E., Liontos, N., Gregor, K., Jones, P. B., & SOHO Study Group (2003). The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta psychiatrica Scandinavica. Supplementum, (416), 16–23. https://doi.org/10.1034/j.1600-0447.107.s416.5.x

Haro, J. M., Suarez, D., Novick, D., Brown, J., Usall, J., Naber, D., & SOHO Study Group (2007). Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: observational versus randomized studies results. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology, 17(4), 235–244. https://doi.org/10.1016/j.euroneuro.2006.09.005

Hochberg, Y. (1988). A Sharper Bonferroni Procedure for Multiple Tests of Significance. Biometrika, 75(4), 800-802. http://dx.doi.org/10.1093/biomet/75.4.800

Honer, W. G., Thornton, A. E., Sherwood, M., MacEwan, G. W., Ehmann, T. S., Williams, R., Kopala, L. C., Procyshyn, R., & Barr, A. M. (2007). Conceptual and methodological issues in the design of clinical trials of antipsychotics for the treatment of schizophrenia. CNS drugs, 21(9), 699–714. https://doi.org/10.2165/00023210-200721090-00001

Howes, O. D., McCutcheon, R., Agid, O., de Bartolomeis, A., van Beveren, N. J., Birnbaum, M. L., Bloomfield, M. A., Bressan, R. A., Buchanan, R. W., Carpenter, W. T., Castle, D. J., Citrome, L., Daskalakis, Z. J., Davidson, M., Drake, R. J., Dursun, S., Ebdrup, B. H., Elkis, H., Falkai, P., Fleischacker, W. W., … Correll, C. U. (2017). Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. The American journal of psychiatry, 174(3), 216–229. https://doi.org/10.1176/appi.ajp.2016.16050503

Ioannidis J. P. (2009). Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne, 181(8), 488–493. https://doi.org/10.1503/cmaj.081086

Iversen, T. S. J., Steen, N. E., Dieset, I., Hope, S., Mørch, R., Gardsjord, E. S., Jørgensen, K. N., Melle, I., Andreassen, O. A., Molden, E., & Jönsson, E. G. (2018). Side effect burden of antipsychotic drugs in real life - Impact of gender and polypharmacy. Progress in neuro-psychopharmacology & biological psychiatry, 82, 263–271. https://doi.org/10.1016/j.pnpbp.2017.11.004

Johnson D. A. (2009). Historical perspective on antipsychotic long-acting injections. The British journal of psychiatry. Supplement, 52, S7–S12. https://doi.org/10.1192/bjp.195.52.s7

Josiassen, R. C., Joseph, A., Kohegyi, E., Stokes, S., Dadvand, M., Paing, W. W., & Shaughnessy, R. A. (2005). Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. The American journal of psychiatry, 162(1), 130–136. https://doi.org/10.1176/appi.ajp.162.1.130

Kaplan, G., Casoy, J., & Zummo, J. (2013). Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes

of schizophrenia. Patient preference and adherence, 7, 1171–1180. https://doi.org/10.2147/PPA.S53795

Kasteridis, P., Ride, J., Gutacker, N., Aylott, L., Dare, C., Doran, T., Gilbody, S., Goddard, M., Gravelle, H., Kendrick, T., Mason, A., Rice, N., Siddiqi, N., Williams, R., & Jacobs, R. (2019). Association Between Antipsychotic Polypharmacy and Outcomes for People With Serious Mental Illness in England. Psychiatric services (Washington, D.C.), 70(8), 650–656. https://doi.org/10.1176/appi.ps.201800504

Katona, L., Bitter, I., & Czobor, P. (2021). A meta-analysis of effectiveness of real-world studies of antipsychotics in schizophrenia: Are the results consistent with the findings of randomized controlled trials?. Translational psychiatry, 11(1), 510. https://doi.org/10.1038/s41398-021-01636-9

Katona, L., Czobor, P., & Bitter, I. (2014). Real-world effectiveness of antipsychotic monotherapy vs. polypharmacy in schizophrenia: to switch or to combine? A nationwide study in Hungary. Schizophrenia research, 152(1), 246–254. https://doi.org/10.1016/j.schres.2013.10.034

Katz R. (2004). FDA: evidentiary standards for drug development and approval. NeuroRx: the journal of the American Society for Experimental NeuroTherapeutics, 1(3), 307–316. https://doi.org/10.1602/neurorx.1.3.307

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia bulletin, 13(2), 261–276. https://doi.org/10.1093/schbul/13.2.261

Kay, S. R., Opler, L. A., & Lindenmayer, J. P. (1988). Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry research, 23(1), 99–110. https://doi.org/10.1016/0165-1781(88)90038-8

Kay, S. R., Opler, L. A., & Lindenmayer, J. P. (1989). The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. The British journal of psychiatry. Supplement, (7), 59–67.

Keepers, G. A., Fochtmann, L. J., Anzia, J. M., Benjamin, S., Lyness, J. M., Mojtabai, R., Servis, M., Walaszek, A., Buckley, P., Lenzenweger, M. F., Young, A. S., Degenhardt, A., Hong, S. H., & (Systematic Review) (2020). The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. The

American journal of psychiatry, 177(9), 868–872. https://doi.org/10.1176/appi.ajp.2020.177901

Kilzieh, N., Todd-Stenberg, J. A., Kennedy, A., Wood, A. E., & Tapp, A. M. (2008). Time to discontinuation and self-discontinuation of olanzapine and risperidone in patients with schizophrenia in a naturalistic outpatient setting. Journal of clinical psychopharmacology, 28(1), 74–77. https://doi.org/10.1097/jcp.0b013e3181602cf3

Kirkpatrick, B., Fenton, W. S., Carpenter, W. T., Jr, & Marder, S. R. (2006). The NIMH-MATRICS consensus statement on negative symptoms. Schizophrenia bulletin, 32(2), 214–219. https://doi.org/10.1093/schbul/sbj053

Kishimoto, T., Hagi, K., Nitta, M., Kane, J. M., & Correll, C. U. (2019). Long-term effectiveness of oral second-generation antipsychotics in patients with schizophrenia and related disorders: a systematic review and meta-analysis of direct head-to-head comparisons. World psychiatry: official journal of the World Psychiatric Association (WPA), 18(2), 208–224. https://doi.org/10.1002/wps.20632

Kishimoto, T., Robenzadeh, A., Leucht, C., Leucht, S., Watanabe, K., Mimura, M., Borenstein, M., Kane, J. M., & Correll, C. U. (2014). Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. Schizophrenia bulletin, 40(1), 192–213. https://doi.org/10.1093/schbul/sbs150

Krause, M., Huhn, M., Schneider-Thoma, J., Rothe, P., Smith, R. C., & Leucht, S. (2018). Antipsychotic drugs for elderly patients with schizophrenia: A systematic review and meta-analysis. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology, 28(12), 1360–1370. https://doi.org/10.1016/j.euroneuro.2018.09.007

Lähteenvuo, M., & Tiihonen, J. (2021). Antipsychotic Polypharmacy for the Management of Schizophrenia: Evidence and Recommendations. Drugs, 81(11), 1273–1284. https://doi.org/10.1007/s40265-021-01556-4

Lally, J., & MacCabe, J. H. (2015). Antipsychotic medication in schizophrenia: a review. British medical bulletin, 114(1), 169–179. https://doi.org/10.1093/bmb/ldv017

Lally, J., Ajnakina, O., Di Forti, M., Trotta, A., Demjaha, A., Kolliakou, A., Mondelli, V., Reis Marques, T., Pariante, C., Dazzan, P., Shergil, S. S., Howes, O. D., David, A. S., MacCabe, J. H., Gaughran, F., & Murray, R. M. (2016). Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia

spectrum psychoses. Psychological medicine, 46(15), 3231–3240. https://doi.org/10.1017/S0033291716002014

Langan, J., Mercer, S. W., & Smith, D. J. (2013). Multimorbidity and mental health: can psychiatry rise to the challenge?. The British journal of psychiatry: the journal of mental science, 202, 391–393. https://doi.org/10.1192/bjp.bp.112.123943

Lehman, A. F., Lieberman, J. A., Dixon, L. B., McGlashan, T. H., Miller, A. L., Perkins, D. O., Kreyenbuhl, J., American Psychiatric Association, & Steering Committee on Practice Guidelines (2004). Practice guideline for the treatment of patients with schizophrenia, second edition. The American journal of psychiatry, 161(2 Suppl), 1–56.

Lehrer, D. S., & Lorenz, J. (2014). Anosognosia in schizophrenia: hidden in plain sight. Innovations in clinical neuroscience, 11(5-6), 10–17.

Leucht, S., Arango, C., Fleischhacker, W. W., Kapur, S., Stroup, S., van Os, J., Correll, C. U. (2013). CINP Schizophrenia Guidelines. Retrieved 2022. November 10. from https://www.cinp.org/resources/Documents/CINP-schizophrenia-guideline-24.5.2013-A-C-method.pdf.

Lim, K., Peh, O. H., Yang, Z., Rekhi, G., Rapisarda, A., See, Y. M., Rashid, N. A. A., Ang, M. S., Lee, S. A., Sim, K., Huang, H., Lencz, T., Lee, J., & Lam, M. (2021). Large-scale evaluation of the Positive and Negative Syndrome Scale (PANSS) symptom architecture in schizophrenia. *Asian journal of psychiatry*, *62*, 102732. https://doi.org/10.1016/j.ajp.2021.102732

Lin, C. H., Kuo, C. C., Chou, L. S., Chen, Y. H., Chen, C. C., Huang, K. H., & Lane, H. Y. (2010). A randomized, double-blind comparison of risperidone versus low-dose risperidone plus low-dose haloperidol in treating schizophrenia. Journal of clinical psychopharmacology, 30(5), 518–525. https://doi.org/10.1097/JCP.0b013e3181f28dff

McCutcheon, R. A., Reis Marques, T., & Howes, O. D. (2020). Schizophrenia-An Overview. JAMA psychiatry, 77(2), 201–210. https://doi.org/10.1001/jamapsychiatry.2019.3360

Mohamed, S., Rosenheck, R., Harpaz-Rotem, I., Leslie, D., & Sernyak, M. J. (2009). Duration of pharmacotherapy with long-acting injectable risperidone in the treatment of schizophrenia. The Psychiatric quarterly, 80(4), 241–249. https://doi.org/10.1007/s11126-009-9111-9

Muench, J., & Hamer, A. M. (2010). Adverse effects of antipsychotic medications. American family physician, 81(5), 617–622.

NICE Guideline CG178. Psychosis and schizophrenia in adults: prevention and management. (2014). National Institute for Health and Care Excellence (NICE). Retrieved 2022. November 10. from https://www.nice.org.uk/guidance/cg178

Nordon, C., Karcher, H., Groenwold, R. H., Ankarfeldt, M. Z., Pichler, F., Chevrou-Severac, H., Rossignol, M., Abbe, A., Abenhaim, L., & GetReal consortium (2016). The "Efficacy-Effectiveness Gap": Historical Background and Current Conceptualization. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research, 19(1), 75–81. https://doi.org/10.1016/j.jval.2015.09.2938

Oosthuizen, P., Emsley, R., Jadri Turner, H., & Keyter, N. (2004). A randomized, controlled comparison of the efficacy and tolerability of low and high doses of haloperidol in the treatment of first-episode psychosis. The international journal of neuropsychopharmacology, 7(2), 125–131. https://doi.org/10.1017/S1461145704004262

Østergaard, S. D., Opler, M. G. A., & Correll, C. U. (2017). Bridging the Measurement Gap Between Research and Clinical Care in Schizophrenia: Positive and Negative Syndrome Scale-6 (PANSS-6) and Other Assessments Based on the Simplified Negative and Positive Symptoms Interview (SNAPSI). Innovations in clinical neuroscience, 14(11-12), 68–72.

Ostuzzi, G., Bighelli, I., So, R., Furukawa, T. A., & Barbui, C. (2017). Does formulation matter? A systematic review and meta-analysis of oral versus long-acting antipsychotic studies. Schizophrenia research, 183, 10–21. https://doi.org/10.1016/j.schres.2016.11.010

Overall, J. E. (1974) The brief psychiatric rating scale in psychopharmacology research. In Pichot, P. and Oliver-Martin, R. (eds.), Psychological Measurements in Psychopharmacology: Modern Problems in Pharmacopsychiatry. (pp. 67–78.) https://www.karger.com/Article/Abstract/395069#

Rosenheck, R. A., Davis, S., Covell, N., Essock, S., Swartz, M., Stroup, S., McEvoy, J., & Lieberman, J. (2009). Does switching to a new antipsychotic improve outcomes? Data from the CATIE Trial. Schizophrenia research, 107(1), 22–29. https://doi.org/10.1016/j.schres.2008.09.031

Rupnow, M. F., Greenspan, A., Gharabawi, G. M., Kosik-Gonzalez, C., Zhu, Y., & Stahl, S. M. (2007). Incidence and costs of polypharmacy: data from a randomized, double-blind, placebo-controlled study of risperidone and quetiapine in patients with schizophrenia or schizoaffective disorder. Current medical research and opinion, 23(11), 2815–2822. https://doi.org/10.1185/030079907x233359

Samara, M. T., Dold, M., Gianatsi, M., Nikolakopoulou, A., Helfer, B., Salanti, G., & Leucht, S. (2016). Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. JAMA psychiatry, 73(3), 199–210. https://doi.org/10.1001/jamapsychiatry.2015.2955

Samara, M. T., Nikolakopoulou, A., Salanti, G., & Leucht, S. (2019). How Many Patients With Schizophrenia Do Not Respond to Antipsychotic Drugs in the Short Term? An Analysis Based on Individual Patient Data From Randomized Controlled Trials. Schizophrenia bulletin, 45(3), 639–646. https://doi.org/10.1093/schbul/sby095

Sampson, S., Hosalli, P., Furtado, V. A., & Davis, J. M. (2016). Risperidone (depot) for schizophrenia. The Cochrane database of systematic reviews, 4, CD004161. https://doi.org/10.1002/14651858.CD004161.pub2

Sekhon, J. S. (2011). Multivariate and Propensity Score Matching Software with Automated Balance Optimization: The Matching package for R. Journal of Statistical Software, 42(7), 1–52. https://doi.org/10.18637/jss.v042.i07

Smith, D. J., Langan, J., McLean, G., Guthrie, B., & Mercer, S. W. (2013). Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. BMJ open, 3(4), e002808. https://doi.org/10.1136/bmjopen-2013-002808

Soares-Weiser, K., Béchard-Evans, L., Lawson, A. H., Davis, J., & Ascher-Svanum, H. (2013). Time to all-cause treatment discontinuation of olanzapine compared to other antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology, 23(2), 118–125. https://doi.org/10.1016/j.euroneuro.2012.05.001

Stroup, T. S., & Gray, N. (2018). Management of common adverse effects of antipsychotic medications. World psychiatry: official journal of the World Psychiatric Association (WPA), 17(3), 341–356. https://doi.org/10.1002/wps.20567

Takács, P., Czobor, P., Fehér, L., Gimesi-Országh, J., Fadgyas-Freyler, P., Bacskai, M., Rakonczai, P., Borsi, A., Hegyi, R., Németh, T., Sermon, J., & Bitter, I. (2019). Comparative effectiveness of second generation long-acting injectable antipsychotics based on nationwide database research in Hungary. PloS one, 14(6), e0218071. https://doi.org/10.1371/journal.pone.0218071

Tiihonen, J., Haukka, J., Taylor, M., Haddad, P. M., Patel, M. X., & Korhonen, P. (2011). A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. The American journal of psychiatry, 168(6), 603–609. https://doi.org/10.1176/appi.ajp.2011.10081224

Tiihonen, J., Mittendorfer-Rutz, E., Majak, M., Mehtälä, J., Hoti, F., Jedenius, E., Enkusson, D., Leval, A., Sermon, J., Tanskanen, A., & Taipale, H. (2017). Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29 823 Patients With Schizophrenia. JAMA psychiatry, 74(7), 686–693. https://doi.org/10.1001/jamapsychiatry.2017.1322

Tiihonen, J., Taipale, H., Mehtälä, J., Vattulainen, P., Correll, C. U., & Tanskanen, A. (2019). Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia. JAMA psychiatry, 76(5), 499–507. https://doi.org/10.1001/jamapsychiatry.2018.4320

Tiihonen, J., Wahlbeck, K., Lönnqvist, J., Klaukka, T., Ioannidis, J. P., Volavka, J., & Haukka, J. (2006). Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ (Clinical research ed.), 333(7561), 224. https://doi.org/10.1136/bmj.38881.382755.2F

White Junod, S. (2008) FDA and Clinical Drug Trials: A Short History. In A Quick Guide to Clinical Trials, Davies, M. and Kerimani, F. (eds.) Bioplan, Inc. (pp. 25-55.) Retrieved 2022. November 10. from https://www.fda.gov/media/110437/download

9. Bibliography of the candidate's publications

9.1. Bibliography of the candidate's publications related to the thesis

Katona, L., Bitter, I., & Czobor, P. (2021). A meta-analysis of effectiveness of real-world studies of antipsychotics in schizophrenia: Are the results consistent with the findings of randomized controlled trials?. Translational psychiatry, 11(1), 510. https://doi.org/10.1038/s41398-021-01636-9

Katona, L., Czobor, P., & Bitter, I. (2014). Real-world effectiveness of antipsychotic monotherapy vs. polypharmacy in schizophrenia: to switch or to combine? A nationwide study in Hungary. Schizophrenia research, 152(1), 246–254. https://doi.org/10.1016/j.schres.2013.10.034

9.2 Bibliography of the candidate's publications not related to the thesis

Balogh, S., Papp, R., Katona, L., Császár, A. (2010) Csökkenő kardiovaszkuláris mortalitás Magyarországon - a kardiometabolikus gyógyszeres terápia hatásának vizsgálata [Falling cardiovascular mortality in Hungary: an examination of the effects of cardiometabolic drug therapy]. Orvostovábbképző Szemle. 17(10), 13-21.

Bitter, I., Katona, L., Zámbori, J., Takács, P., Fehér, L., Diels, J., Bacskai, M., Lang, Z., Gyáni, G., & Czobor, P. (2013). Comparative effectiveness of depot and oral second generation antipsychotic drugs in schizophrenia: a nationwide study in Hungary. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology, 23(11), 1383–1390. https://doi.org/10.1016/j.euroneuro.2013.02.003

Folyovich, A., Béres-Molnár K, A., Gimesi-Országh, J., Katona, L., Biczó, D., Vörös, K., Gőbl, G., Ajtay, A., & Bereczki, D.,(2018). Is stroke indeed a "Monday morning disease"? A stroke valóban hétfő reggeli betegség? Ideggyogyaszati szemle, 71(5-06), 161–168. https://doi.org/10.18071/isz.71.0161

Jermendy, G., Wittmann, I., Nagy, L., Kiss, Z., Rokszin, G., Abonyi-Tóth, Z., Katona, L., Paragh, G., Karádi, I., & Merkely, B. (2012). Persistence of initial oral antidiabetic treatment in patients with type 2 diabetes mellitus. Medical science monitor: international medical journal of experimental and clinical research, 18(2), CR72–CR77. https://doi.org/10.12659/msm.882459

Katona, L., Molnár, M. P. (2010) Az OEP elemzéshez kötött statisztikai adatszolgáltatása [Statistical analysis service related to the National Health Insurance Fund Administration of Hungary]. IME. 9 (Special edition in health economics), 42-46.

Kozma, P. O., Katona, L., Zámbori, J., Dankó, D., Molnár, M. P. (2010) A szkizofréniában szenvedô, antipszichotikus terápiában részesülô járóbeteg-populáció elemzése gyógyszer- és betegforgalmi adatok alapján a 2005-2008-as idôszakban [Analysis of outpatient schizophrenia sufferers taking part in antipsychotic treatment on the basis of pharmaceutical sales and patient turnover from 2005 through 2008]. IME. 9(6), 16-22.

Lester, J. F., Casbard, A. C., Al-Taei, S., Harrop, R., Katona, L., Attanoos, R. L., Tabi, Z., & Griffiths, G. O. (2018). A single centre phase II trial to assess the immunological activity of TroVax® plus pemetrexed/cisplatin in patients with malignant pleural

mesothelioma - the SKOPOS trial. Oncoimmunology, 7(12), e1457597. https://doi.org/10.1080/2162402X.2018.1457597

Moldvay, J., Rokszin, G., Abonyi-Tóth, Z., Katona, L., Fábián, K., & Kovács, G. (2015). Lung cancer drug therapy in Hungary - 3-year experience. OncoTargets and therapy, 8, 1031–1038. https://doi.org/10.2147/OTT.S65794

Szabó, M., Katona, L., Nádudvari, N., Dankó, D., Molnár, M. P. (2011) A generikus penetráció ösztönzésének „puha" eszközei a clopidogrel hatóanyag példáján ["Soft" promotion tools for generic penetration using the example of the active ingredient clopidogrel]. IME. 10 (Special edition in health economics), 14-21.

Tomcsányi, J., Bózsik, B., Rokszin, G., Abonyi-Tóth, Z., & Katona, L. (2012). A pitvarfibrilláció prevalenciája Magyarországon [The prevalence of atrial fibrillation in Hungary]. Orvosi hetilap, 153(9), 339–342. https://doi.org/10.1556/OH.2012.29305

10. Acknowledgements

First and foremost, I am extremely grateful to my supervisor, Dr. Pál Czobor, for his invaluable advice, continuous support, motivation and patience during my PhD study. His immense knowledge and plentiful experience have encouraged me in all the time of my academic research.

Besides my advisor, a special thank you to Professor István Bitter, former chair of Department of Psychiatry and Psychotherapy at Semmelweis University, for providing his professional support and advices.

Finally, but the most importantly, I would like to thank my family for supporting me throughout writing this thesis and my life in general.