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Comparative effectiveness of depot and oral second generation antipsychotic drugs in schizophrenia: A nationwide study in Hungary

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Abstract
We conducted a nationwide, full-population based investigation to evaluate the comparative effectiveness of all marketed second generation antipsychotic drugs (SGA) prescribed for outpatients with the diagnosis of schizophrenia in Hungary. Using the national central register, our observational follow-up study included all patients with schizophrenia or related disorder between 01/01/2006 and 30/06/2008. The study cohort comprised 9567 patients who started new SGA during the inclusion period (01/07/2007–30/06/2008). All-cause medication discontinuation of 8 SGAs (1 depot and 7 oral formulations) marketed during the inclusion period, and the time to all-cause discontinuation were the main outcomes. Statistical models included the Kaplan–Meier and the Cox proportional hazards models with propensity score adjustment. Patients treated with a depot formulation risperidone had the longest time to discontinuation with a median of 215 days (95%CI:181–242 days), which was statistically significantly different compared to patients treated with the rest of the medications: olanzapine (136 days, 95%CI:121–153 days), aripiprazole (102 days, 95%CI:81–126 days), ziprasidone (93 days, 95%CI:82–119 days), quetiapine (89 days, 95%CI:81–100 days), clozapine (76 days, 95%CI:54–92 days), amisulpride (73 days, 95%CI:62–85 days), and risperidone (55 days, 95%CI: 41–63 days). Our results in Hungary are partly similar to those of a recent register-based study in Finland

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with patients who were discharged from their first hospitalization for schizophrenia (Tiihonen et al., 2006, 2011); namely the median times to all-cause medication discontinuation were <120 days for the majority of the oral SGA. In terms of medication differences, our data support the superior effectiveness of the depot formulation regarding all-cause discontinuation, followed by olanzapine at the efficacy rank order.

1. Introduction

Oral formulations of second generation antipsychotic drugs (SGA) have been introduced in the last two decades and recently they were followed by long-acting formulations (Kane et al., 2003; Lauriello et al., 2008). Several clinical trials addressed the effectiveness of SGA as compared to the first generation antipsychotic drugs (FGA) (Lieberman et al., 2005; Kahn et al., 2008). Additional studies focused on the effectiveness of antipsychotic drugs under real-life conditions (Kelin et al., 2011; Swartz et al., 2005). Some of these studies, especially by Medicare/Medicaid groups in the U.S. (Chen et al., 2008; Zhao et al., 2004), aimed to mimic clinical studies in order to examine the superiority of SGA over FGA and to investigate whether there is a difference in effectiveness among the various SGA.

There is a scarcity of data on the comparative effectiveness of depot antipsychotics. Leucht et al. (2011) could identify only 10 randomized studies that compared intramuscular depot with oral formulations of antipsychotic drugs in people with schizophrenia or related disorders in long-term studies defined as 1 year or longer (Leucht et al., 2011). A more recent meta-analysis including 21 randomized controlled studies (RCTs) found that oral and depot formulations of antipsychotics were similar for relapse prevention and the authors emphasized, that RCTs are less representative of real-world patients than naturalistic studies and called for further studies with "real word" patients (Kishimoto et al., 2013).

Hungary is one of the few countries where the access to health care data is guaranteed by law. Its health care system is predominantly state owned: the National Health Insurance Fund (NHIF) covers 100% of the population of 10 million inhabitants. NHIF provides de-identified patient data on healthcare services and major medical outcomes.

Through a collaboration of Academia (Department of Psychiatry and Psychotherapy, Semmelweis University), the payer (NHIF), the pharmaceutical industry (Janssen-Cilag Hungary and EMEA) and an independent consulting company (Healthware Ltd) we conducted a study to investigate the population of patients with schizophrenia in Hungary. The analyses were conducted by an independent biostatistician (LK) who worked for the government agency (the payer, NHIF). Our aim was to evaluate the comparative effectiveness of the SGA marketed in Hungary in a defined study period.

2. Experimental procedures

2.1. Data, study design and patient population

This was a parallel-group, register-based observational follow-up study of all patients in Hungary who

(1) had at least one record of schizophrenia diagnosis (F20.0-F20.9 according to the International Classification of Diseases, 10th revision ICD-10) (World Health Organization, 1992) between 01/01/2006 and 30/06/2008 (patient pool), and
(2) had been initiated on a new antipsychotic drug as monotherapy during the inclusion period of 01/07/2007 and 30/06/2008 (study population).

A new antipsychotic drug was defined as no prescription of the same compound during the previous 6 months.

No further criteria were applied; the broad inclusion criteria aimed to increase the generalizability of the findings to treatment in usual-care settings using the register of the NHIF. This register allows identifying all patients in Hungary with a record of any reimbursed drug prescription since 1998. Information on patient-related events, including therapy discontinuation, switch to a new medication, hospitalization, co-morbidity and mortality are recorded in the system both for inpatient and outpatient care.

2.2. Study periods and treatment groups

We studied the relative effectiveness of widely used oral and depot SGAs prescribed as monotherapy for outpatients with the schizophrenia diagnosis. In the nation-wide cohort of patients with schizophrenia in Hungary that we investigated, second generation antipsychotics constitute the majority of the total antipsychotic market (market share=63%). The minority share of the market (37%) by the first generation antipsychotics (FGA) was distributed among considerably more medications than in the case of SGA, which would have made the comparison of the individual FGAs infeasible.

Monotherapy was defined as only one antipsychotic prescription at the day of therapy initiation, and no further prescription during the next 30 days (except for temporary oral supplementation at the initiation of Risperidone Long-Acting Injectable [RLAI] or dose increase). Only those SGAs were excluded from the study that were either not available during the whole inclusion period (paliperidone), or were used by only a small number of patients (sertindole and zotepine, $n<25$). The top part of Fig. 1 displays the study periods, whereas the bottom part (in red) shows the inclusion process and study procedures for a particular patient.

During the 1-year inclusion period, all patients were included who (a) started a new monotherapy (Day 1 in the inclusion period) between 01/07/2007 and 30/06/2008 and (b) had no other FGA or SGA prescription for the subsequent 30 days. In order to be classified as new monotherapy, no prior prescription of the same compound was allowed during the previous 6 months, which was confirmed in the retrospective period (Fig. 1). All included patients were observed for 365 days from Day 1 (observation period).

The investigation had eight parallel treatment groups focusing on the eight most frequently used SGA in the country, confirmed by sales records for the years 2008 and 2009. These medications included the following seven oral SGA: amisulpride (AMIS), aripiprazole (ARIP), clozapine (CLOZ), olanzapine (OLAN), quetiapine (QUET), risperidone (RISP), and ziprasidone (ZIPR), and one