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Real-world effectiveness of antipsychotic monotherapy vs. polypharmacy in schizophrenia: To switch or to combine? A nationwide study in Hungary

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ABSTRACT

Background: Leading guidelines recommend antipsychotic (AP) monotherapy for schizophrenia, nonetheless the combination of antipsychotics (polypharmacy) is common practice worldwide. We conducted a nationwide population-based study to investigate the comparative effectiveness of monotherapy versus polypharmacy in schizophrenia and other psychotic disorders.

Methods: Data was collected from the Hungarian National Health Insurance Fund's database and a non-interventional retrospective–prospective parallel arm study was designed with a monotherapy arm (MA, switch to a new antipsychotic after >60 days of monotherapy, N = 5480) and a polypharmacy arm with two APs (PA, addition of a second antipsychotic after >60 days of monotherapy, N = 7901). The analyses focused on therapy changers, who started a new monotherapy or added a new AP to the existing one. Polypharmacy combinations with more than two APs were not investigated. Fourteen APs were investigated representing the majority of marketed antipsychotics of Hungary in the period of 1/2007–12/2009. The principal endpoint was the time to all-cause treatment discontinuation during a one-year observation period. Kaplan–Meier survival analysis and Cox proportional hazards model were applied with propensity score adjustment.

Results: The principal outcome measure time to all-cause discontinuation indicated superiority for monotherapy over polypharmacy for the majority of (oral and depot) second generation APs (SGAs). For first generation APs (FGAs), oral formulations did not show a difference between monotherapy and polypharmacy, while depot formulations exhibited polypharmacy advantage. For the four most frequently used oral SGAs, the median times to all-cause discontinuation for monotherapy and polypharmacy, respectively, were 192 and 100 days for aripiprazole; 222 and 86 days for olanzapine; 176 and 91 days for quetiapine; and 157 and 93 days for risperidone. For mortality and hospitalization, a significant overall advantage of polypharmacy was detected.

Conclusions: Our study provides evidence for the superiority of monotherapy over polypharmacy for SGAs in terms of all-cause treatment discontinuation in schizophrenia. Polypharmacy, however, was associated with a lower likelihood of mortality and hospitalizations. The finding that MA is superior to PA 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.

1. Introduction

Despite the general recommendation of using antipsychotic monotherapy in the treatment of schizophrenia and other psychotic disorders (Lehman et al., 2004; Freedman, 2005; NICE, 2009) the use of a combination of antipsychotics (polypharmacy) is widely applied in clinical practice (Faries et al., 2005; Honer et al., 2007; Barnes and Paton, 2011; Ballon and Stroup, 2013). However, clinical evidence regarding its comparative effectiveness in schizophrenia against monotherapy is scarce (Josiassen et al., 2005; Rupnow et al., 2007; Rosenheck et al., 2009; Essock et al., 2011; Ascher-Svanum et al., 2012; Fleischhacker and Uchida, 2012), and guidelines typically recommend it as a last resort. Previous clinical trials addressing this issue had certain shortcomings, including small sample sizes; short follow-up periods; use of endpoints not directly applicable for clinical practice, issues with study design (e.g., lack of randomization or blinding); and comparison of only a few treatments with no head-to-head comparisons between various medications (Josiassen et al., 2005; Rupnow et al., 2007; Essock et al., 2011).

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Observational studies investigating effectiveness had larger sample sizes, longer observation periods, clinically relevant endpoints and head-to-head treatment comparisons. Nonetheless, they also have shortcomings, e.g. lack of randomization, and may be subject to certain biases, including selection bias (Faries et al., 2005; Kreyenbuhl et al., 2006; Barbui et al., 2009; Ascher-Svanum et al., 2012). While meta-analyses (Barbui et al., 2009; Correll et al., 2009) and systematic reviews (Honer et al., 2007; Tranulis et al., 2008; Cipriani et al., 2009; Barnes and Paton, 2011; Fleischhacker and Uchida, 2012) of individual clinical trials usually bring together evidence using data collected in many countries, and include large number of patients, they have certain limitations including the heterogeneity in study design, clinical outcomes, and differences by country and geographical region in how long patients with schizophrenia are taking their antipsychotic medication (Bitter et al., 2008; Barbui et al., 2009; Correll et al., 2009). Although the majority of currently available studies do not specifically address polypharmacy's effectiveness against monotherapy, their results are important since they provide basic information about time to all-cause discontinuation of individual medications in monotherapy (Lieberman et al., 2005; Stroup et al., 2006; Tiihonen et al., 2006; Chen et al., 2008; Kahn et al., 2008; Rosenheck et al., 2011).

Time to all-cause discontinuation has been widely accepted as a clinically relevant measure of effectiveness by combining efficacy and tolerability (Lieberman et al., 2005; Kahn et al., 2008). Lawmakers, regulatory agencies and academic researchers (Ballon and Stroup, 2013) acknowledge the value of naturalistic and observational studies (Food and Drug Administration, 2007; Federal Coordinating Council, 2009). Nationwide databases may be helpful in identifying treatment patterns and effectiveness of treatment strategies and uncovering rare events related to treatment.

Our nationwide non-interventional retrospective–prospective study seeks to compare the effectiveness of antipsychotic monotherapy versus polypharmacy.

2. Methods

2.1. Subjects

Subjects were selected on the basis of antipsychotic (AP) dispensation over a three-year period from January 1st, 2007 to December 31st, 2009. Patients of any age were eligible provided they had at least one valid record of AP dispensation and a chart diagnosis of schizophrenia or schizoaffective disorder with an ICD code (World Health Organization, 1992) of F2X in the majority (≥67%) of prescriptions.

2.2. Data collection

Patient-level data were selected from the centralized national insurance database of Hungary, which includes dispensation records for all drugs reimbursed by NHIF and records of all inpatient, outpatient, and other services occurring within and funded by the national health system. All antipsychotics marketed in the country are practically fully reimbursed (for a fee of ca. $1.30/box). The database contains information about the unique identifier of the prescription drug, unique patient ID, dispensation date and quantity, and the prescription's ICD code.

2.3. Procedures

To assure comparable treatment groups (MA and PA), we selected patients subjected to therapy switch from monotherapy to either different monotherapy or to polypharmacy (addition of a second antipsychotic to the existing one; patients who used more than two APs simultaneously were not investigated in PA). Eligible patients were included after therapy change in the MA if they continue to receive the newly assigned monotherapy for >60 days; and in the PA if the combined treatment with the two antipsychotics continued for >60 days. This criterion served to exclude transient polypharmacies (≤60 days (Treatment of schizophrenia, 1999; Faries et al., 2005); e.g., during switch from one monotherapy to another), and to provide an equal baseline condition for both arms. In sensitivity analyses using a 30 and 90 days cut-off, respectively, we investigated whether the choice of the threshold criterion (60 days) had an impact on our results. All patients were included when they first fulfilled the eligibility criteria for the study.

Estimation of treatment duration for the 14 active compounds, based on 168 dosing forms defined by the combination of tablet or depot strengths and quantity in the pill-box, included a two-step procedure. First, based on patient prescription records, median days between the date of treatment dispensations were determined (omitting outliers, defined as ≥120 days). Second, based on all individual medians, we calculated the overall median for the entire population. The total number of treatment days for each medication was defined as the sum of subsequent, concatenated treatment periods, including grace periods (<60 days). Presence of polypharmacy for each day during the observation period was determined based on individual treatment intervals superimposed on each other.

2.4. Statistical analyses

2.4.1. Variables

The principal outcome measure was all-cause discontinuation defined by the following events: discontinuation of treatment, switching to other AP medication, initiation of concomitant new AP as add-on therapy, discontinuation of either one of two medications in the PA, hospitalization to psychiatric ward or institute ('psychiatric hospitalization'), or death due to any reason. The rationale for including psychiatric hospitalization among the events for discontinuation is that no information was available for the drugs given during hospital treatment, and it is likely that medication changes (especially add-on) occurred in many cases in order to provide better control of symptoms during this period. A more detailed breakdown for mortality, i.e., death by natural and unnatural causes was not possible due to insufficient database resolution. Psychiatric hospitalization and mortality were also used as secondary outcome measures in separate analyses.

The main independent variable of interest was the study arm (MA or PA).

2.4.2. Statistical models

At the first level of analysis, we applied a non-parametric approach, the Kaplan–Meier model for survival analysis to determine the median time to discontinuation during the one-year observation period. For inferential statistical analysis we used the Cox proportional-hazards regression model (Cox, 1972). At the second level, for group comparisons we used the risk ratio (hazard ratio, HR) statistics. To investigate the effectiveness of monotherapy vs. polypharmacy we conducted pairwise comparisons for all APs used in the MA on one hand, and all PAs which included that specific AP as part of a combination on the other. To eliminate demographic or clinical differences between the study groups we conducted matched-pair (Sekhon, 2011) analyses with propensity score matching using the Cox proportional-hazards regression model for clustered data based on the matched pairs. In the case of mortality analyses where the low number events in the individual treatment groups would have made the matched-pair analysis unreliable, we used logistic regressions adjusting for the propensity score as a covariate. For propensity score calculation we performed multivariate logistic regression including gender, age (using both linear and quadratic terms) and number of days of hospitalizations (psychiatric or other wards, respectively) during the 1-year prior study. Using the nonparametric Wilcoxon test, prescriber effect was tested by comparing the ratio of polypharmacy to