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Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia

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ABSTRACT

Introduction: It has remained controversial if antipsychotic treatment is associated with increased or decreased mortality among patients with schizophrenia, and if there are any clinically meaningful differences between specific agents and routes of administration.
Methods: We linked prospectively gathered nationwide register-based data during 2006–2013 to study all-cause mortality among all patients aged 16–64 years with schizophrenia in Sweden ($N = 29{,}823$ in total; $N = 4603$ in the incident cohort). Multivariate Cox regression models were adjusted for clinical and sociodemographic covariates. Sensitivity analyses with the incident cohort were conducted to control for survival bias.
Results: During the mean follow-up of 5.7 years, 2515 patients (8.4%) died. During the maximum follow-up (7.5 years), the lowest cumulative mortality was observed for second generation (SG) long-acting injection (LAI) use (7.5%). Adjusted hazard ratios (aHRs) compared to SG LAI use were 1.37 (95%CI 1.01–1.86) for first generation (FG) LAIs, 1.52 (1.13–2.05) for SG orals, 1.83 (1.33–2.50) for FG orals, and 3.39 (2.53–4.56) for nonuse of antipsychotics. Concerning specific agents, the lowest mortality was observed for once-monthly paliperidone LAI (0.11, 0.03–0.43), oral aripiprazole (0.22, 0.15–0.34), and risperidone LAI (0.31, 0.23–0.43). In pairwise comparison, LAIs were associated with 33% lower mortality than equivalent orals (0.67, 0.56–0.80). The results with incident cohort were consistent with the primary analyses.
Conclusions: Among patients with schizophrenia, LAI use is associated with an approximately 30% lower risk of death compared with oral agents. SG LAIs and oral aripiprazole are associated with the lowest mortality.

1. Introduction

Patients with schizophrenia have a 15–20 year shorter life expectancy than the general population (Laursen et al., 2014), and side effects of antipsychotic medications are considered a putative cause for the excess mortality (Glassman and Bigger Jr., 2001; Liebzeit et al., 2001; Ray et al., 2001; Cheeta et al., 2004; Fergusson et al., 2005; Mackin et al., 2007; Ray et al., 2009; Stahl et al., 2009; Stone et al., 2009). A systematic review suggested that gap in mortality compared with general population is even worsening and may be related to second generation antipsychotic use (Saha et al., 2007). Meta-analysis and systematic reviews of randomized controlled trials (RCTs) suggest that this is not the case, since mortality is lower during use of antipsychotics than during placebo (Baxter et al., 2016; Khan et al., 2007, 2013). However, these trial results have been criticized because the duration of treatments is usually substantially longer for active than placebo arms. Also, trials lasting a few months are too short to assess fatal adverse events related to cumulative drug exposure leading to health problems such as weight gain or diabetes.

Several observational studies on large unselected cohorts have shown that mortality is lower during use of antipsychotic compared with no use (Tiihonen et al., 2006, 2009, 2011, 2012, 2016; Baandrup et al., 2010; Crump et al., 2013; Vanasse et al., 2016). However, these studies either did not control for survival bias or had short follow-up periods which made it difficult to evaluate the comparative effectiveness

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between specific antipsychotics. Further, data on novel agents have been limited, and it is not known whether the route of administration [long-acting injection (LAI) vs. oral] modifies mortality. We aimed to study mortality during specific antipsychotic treatments in a nationwide cohort, also including a large number of first-episode patients to control for survival bias.

2. Materials and methods

This study was based on nationwide data, derived from the Swedish population-based registers. The Regional Ethics Board of Stockholm approved this research project (decision 2007/762–31).

2.1. Study population

All residents aged 16–64 (at year 2006) living in Sweden with registered schizophrenia treatment contact between July 1, 2006 until December 31, 2013 were included in this study. The flow chart of the cohort is shown in Supplementary Fig. 1. In addition to this prevalent cohort, an incident cohort with individuals newly diagnosed with schizophrenia were identified. Schizophrenia diagnosis was based on four registers: the National Patient Register (maintained by the National Board of Health and Welfare) regarding inpatient care since 1988 and specialized outpatient care since 2001, data on disability pension since 1994 and sickness absence since 2005 from the MiDAS register (maintained by the Swedish Social Insurance Agency). All Swedish residents have been assigned a unique personal identification number which enabled linkage between various registers (no missing data). Drug use data since July 2005 was gathered from the Prescribed Drug Register (maintained by the National Board of Health and Welfare) and dates of death were obtained from the Causes of Death Register (maintained by the National Board of Health and Welfare). Demographic characteristics were based on data in the LISA register (maintained by Statistics Sweden).

All individuals with a diagnosis of schizophrenia, schizotypal and delusional disorders [F20–F29 according to the International Classification of Diseases version 10 (ICD-10) classification] were identified from inpatient, specialized outpatient, sickness absence and disability pension (MiDAS) registers and formed the source population ($N = 57{,}256$). An inclusion criterion was diagnosis of schizophrenia (schizophrenia F20 or schizoaffective disorder F25) as main diagnoses in the registers during July 1, 2006 until December 31, 2013 ($N = 33{,}940$ fulfilled this criteria). Based on the exclusion criteria, those aged <16 at cohort entry or over age 64 in 2006 were excluded, leading to the study cohort of 29,823 individuals (prevalent cohort). The incident cohort ($N = 4603$) was defined from the study cohort based on not having a previous main or contributory diagnosis of F20–29 (ICD-10) or 295 (ICD-9) before July 1, 2006 in any of the four databases, and not using antipsychotics between July 1, 2005 and July 1, 2006 according to the Prescribed Drug Register. The cohort entry date was defined as the first diagnosis fulfilling the inclusion criteria (starting from July 1, 2006 for prevalent cases), and individuals were followed up until death or December 31, 2013 (which ever occurred first). This cohort has been used also to study the risk of re-hospitalization and all-cause discontinuation of antipsychotic treatment (Tiihonen et al., 2017).

2.2. Exposure

Antipsychotic use was derived from the Prescribed Drug Register which includes all prescribed dispensed drugs during 2005–2013. Drugs administrated in by healthcare, e.g., during hospitalization are not recorded in the register. Antipsychotics were identified according to the Anatomical Therapeutic Chemical (ATC) classification (WHO) code N05A, excluding lithium (N05AN01). Regarding the package information, antipsychotics were categorized according to drug formulation into oral antipsychotics and long-acting injections (LAI). Further categorization was made into second-generation (SGA) and first-generation (FGA) antipsychotics.

The PRE2DUP method was utilized to model drug use periods from prescription drug purchases (Tanskanen et al., 2015). This method is based on mathematical modelling of drug purchasing behavior for each individual and for each drug substance (ATC code). The method takes into account stockpiling of drugs, dose changes, and periods of hospitalization when drugs are provided by the hospital and not recorded in the drug register. In this method, drug use is controlled with restriction parameters defining the minimum and maximum daily dose for each package (Nordic product number, vnr). When modelling antipsychotics, each drug substance was coded according to drug formulation as oral or LAI, and drug use periods were constructed separately for oral and LAI use. The PRE2DUP method has been utilized previously in studies of antipsychotics (Tiihonen et al., 2009; Taipale et al., 2014; Tolppanen et al., 2016) and validated by expert-opinion on drug use period formation and by comparing it with interview-based medication use data (Taipale et al., 2016).

2.3. Outcomes

The main outcome measure was all-cause mortality.

2.4. Covariates

The multivariate Cox regression models were adjusted for sociodemographic factors, antipsychotic medication use and schizophrenia related factors, other medication use in dependent manner and comorbidities. Comorbid conditions were identified from the National Patient Register (inpatient care and specialized outpatient care) and drug use from the Prescribed Drug Register. For some variables (such as substance abuse), combination of these data sources was used. The exact definitions are provided in the Supplementary Table 1.

2.5. Statistical analyses

We used multivariate-adjusted Cox regression in the analyses. The risk of mortality was compared through the use of two approaches considering time i) on antipsychotic monotherapy only, and ii) on any therapy. In approach i), treatment periods were comprised into a single factor variable indicating either monotherapy of a specified antipsychotic, polytherapy if any two or more antipsychotics were used at the same time, or no use of any antipsychotics. Events and risk time were accounted for a specific antipsychotic only if they occurred during monotherapy of that particular antipsychotic or for polytherapy, if two or more antipsychotics were used at the same time. In approach ii), treatment periods were defined by separate variables for each specific antipsychotic indicating either ongoing treatment or no use of that particular antipsychotic. In this analysis, events and risk time were accounted for a specific antipsychotic whenever that antipsychotic treatment was ongoing (also when used in polytherapy). The difference between these two approaches is described in Supplementary Fig. 2. In these analyses, all deaths were included and deaths in hospitals were considered attributable to the last exposure period in outpatient care. In addition, using otherwise similar approach as in ii), we conducted oral vs. LAI analyses, in which exposure of each antipsychotic with both oral and LAI formulation was comprised into a factor variable with status either no use, oral use or LAI use depending on whether that particular antipsychotic was not used, used orally, or used as LAI, respectively. In these analyses, simultaneous use of oral and LAI was accounted as LAI use (because in pairwise comparisons, oral use was the reference), and polytherapy was a separate variable that was adjusted for when two or more antipsychotics were used simultaneously. For comparison between specific antipsychotics, oral olanzapine was used as a reference drug as it was the most often used drug in the study population.

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