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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.

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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 antipsychotics than during placebo (Tiirilehto 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.
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 1986 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 administered 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 (N05A/N01). 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.
Time dependent Kaplan-Meier curves were constructed for FG-SG and oral-LAI groups. In these curves, patients may contribute to several groups. We conducted sensitivity analyses among the incident cohort in order to control for survival bias. In the comparison of specific antipsychotics (n = 20), the level of significance was set at p < 0.0025.

3. Results

The clinical and sociodemographic characteristics of the prevalent and incident cohorts are described in Supplementary Table 2. During the follow-up (mean 5.7 years, median 6.9 years), 2515 (8.4%) of patients died. The proportions and mean daily doses of used antipsychotics are shown in Supplementary Table 3. Oral olanzapine was most frequently used antipsychotic, followed by oral aripiprazole and oral risperidone in both prevalent and incident cohorts. Of LAIs, zuclopenthixol LAI was most commonly used in prevalent cohort and risperidone LAI in incident cohort.

The adjusted risk of death was 56% lower during use of any antipsychotic compared with no use of antipsychotic (1811 deaths/13,8451 person years versus 704 deaths/32,793 person years (unadjusted HR 0.60, 95% CI 0.55–0.66), adjusted HR 0.44, 95% CI 0.39–0.49, p < 0.0001). Fig. 1 demonstrates the Kaplan-Meier curves of mortality in first (FG) and second (SG) generation oral and long-acting injection (LAI) users compared with no antipsychotic use. Cumulative mortality rates during maximum follow-up of 7.5 years were 7.5% during SG LAI use, 8.5% during SG oral, 12.2% during FG oral, 12.3% during FG LAI, and 15.2% during no use of antipsychotics. Similarly, adjusted risk of death was the lowest during SG-LAI use (Fig. 2).

The mortality rates and data on previous hospitalizations, suicide attempts, and substance abuse for these drug groups are shown in Table 1 for prevalent and incident cohort. The adjusted risks of mortality during monotherapy of specific antipsychotic use in the prevalent cohort (compared with non-use) are shown in Fig. 4. Aripiprazole was the only antipsychotic which differed significantly from oral olanzapine when Bonferroni correction was applied (decreased mortality, p = 0.0003), in addition to no use of antipsychotic (any therapy, including polypharmacy).

Results compared to oral olanzapine as the reference drug (most frequently used medication) in the prevalent cohort are shown in Supplementary Fig. 4. Aripiprazole was the only antipsychotic which differed significantly from oral olanzapine when Bonferroni correction was applied (decreased mortality, p = 0.0003), in addition to no use of antipsychotic (any therapy, including polypharmacy).
antipsychotic which was associated with increased risk of death ($p < 0.0001$).

In the incident cohort, the number of deaths ($n = 152$ total) during specific antipsychotic treatments were too low for meaningful analysis for several specific agents when compared with no use of antipsychotic.

The adjusted HRs were 0.15 (0.04–0.53) for SG LAIs, 0.53 (0.35–0.80) for SG orals, 0.64 (0.34–1.29) for FG LAIs, and 0.66 (0.34–1.29) for FG orals.

Use of any antipsychotic was also associated with substantially lower risk of death (0.54, 0.36–0.80) when compared with no use.

4. Discussion

Our results showed that antipsychotic use was associated with an approximately 50% lower risk of death when compared with no use, which strongly suggests that the net effect on mortality is beneficial. Since medications are started when symptoms re-appear or get worse, it is obvious that the results would be even more favorable for antipsychotic treatment if this bias could be eliminated. Our results are in line with all previous large observational cohort studies (Tiihonen et al., Table 1).
Oral aripiprazole and commonly used LAIs were associated with the lowest mortality both as monotherapy and as any therapy (polypharmacy allowed). Two previous Swedish studies have also reported that aripiprazole is associated with the lowest risk of death, but they did not study mortality for LAIs (Crump et al., 2013; Ringbäck Weitf et al., 2014). These studies used smaller cohorts and shorter follow-up periods, resulting in low statistical power, did not apply Bonferroni correction for multiple comparisons, and did not conduct sensitivity analyses to control for survival bias. However, their results on aripiprazole are well in line with our results. Previous results from large Finnish cohorts (Tiihonen et al., 2009; Kiviniemi et al., 2013) showed the lowest mortality for clozapine, but in the present study clozapine was not among those medications with the best outcomes. This may be related to its more restricted use in Sweden compared to in Finland. It is probable that in Sweden clozapine is used only among the most severely ill patients, and the traditional between-subject analysis used in the comparison of specific antipsychotics may not have been able to fully adjust for the severity of illness. On the other hand, since aripiprazole has little metabolic adverse effects, it may have used frequently among patients with high risk of cardiovascular morbidity, but still it was associated with very low mortality compared with most of the other antipsychotics. Among the commonly used antipsychotics, levomepromazine was associated with the highest mortality, which is in line with previous geriatric and schizophrenia cohort studies (Kiviniemi et al., 2013; Sahlberg et al., 2015; Schmedt et al., 2016; Shi et al., 2007). This discourages the use of levomepromazine either as monotherapy or as combination treatment in schizophrenia.

In the Cox regression analyses, we adjusted for 20 sociodemographic and clinical co-variates such as number of previous hospitalizations, previous and current use of psychotropic and somatic medications, substance abuse, and history of suicidal behavior. Unfortunately, we were not able to adjust for smoking status which is a confounder here. However, the adjusted HR (0.44) was even lower than the unadjusted HR (0.60) in the comparison between antipsychotic use versus no use, which indicates that patients using more antipsychotics have a higher intrinsic risk of death. This suggests that the beneficial effect of antipsychotic use would have been even stronger if residual confounding could have been totally eliminated. Previous literature has reported that patients treated with LAIs more often have substance abuse, more severe psychopathology, and more previous hospitalizations than patients using oral antipsychotics (Shi et al., 2007). This was also seen in our results as patients using LAIs had the highest rate of previous psychiatric hospitalizations, suicide attempts, and substance abuse, and these co-variates were associated with higher risk of death. This implies that patients receiving LAIs might have less healthy life styles in general, and higher levels of morbidity than other patients, which suggests that the superiority of LAIs over orals would have been even more robust if residual confounding could have been totally eliminated.

The relative difference in mortality between any LAI versus equivalent orals was 33% in the total cohort, and the mortality for SG LAIs compared with other drug classes was 27–49% lower in the prevalent cohort and 71–77% lower in the incident cohort. These figures correspond to 2–4% difference in the absolute risk during about 6 years follow-up in the prevalent cohort, and 2% difference during 3.5 years follow-up in the incident cohort. Extrapolation of these results would correspond to about 10% difference in absolute risk in a 15–20 year time span, which suggests that wider use of SG LAIs might result in substantially lower mortality among patients with schizophrenia. Overall, the results show that excess mortality among patients with schizophrenia is more likely associated with a lack of antipsychotic therapy rather than with antipsychotic treatment.

The main strength of this study is nationwide coverage of all schizophrenia patients and their follow-up based on register data covering all residents. We also used data on actually purchased medications instead of data on prescriptions given to the patients. Our results are generalizable to relatively high-income countries with Caucasian populations with all antipsychotic treatments reimbursed by the state. To account for survival bias, we conducted analyses within incident cohort representing new cases. Drug use was modelled with state-of-the-art PRE2DUP method which describes well actual drug use when compared with interview-reported use (Taipale et al., 2016). Use of other medications was treated as continuously updated variables instead of crude baseline estimates allowing better adjustment for time varying conditions.

A limitation was that, despite of adjustment for covariates, all observational studies have residual confounding. However, adjustment for the effects of known clinical and sociodemographic variables indicated that patients using more antipsychotics have a higher intrinsic risk of death. Therefore, it is likely that residual confounding has diluted rather than eliminated the difference in mortality between patients using antipsychotics and those using no antipsychotics.

**Table 1:** Treatment Effect on Mortality

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAI Paliperidone</td>
<td>0.83 (0.49, 1.43)</td>
</tr>
<tr>
<td>Oral Aripiprazole</td>
<td>0.83 (0.49, 1.43)</td>
</tr>
<tr>
<td>LAI Risperidone</td>
<td>0.77 (0.55, 1.09)</td>
</tr>
<tr>
<td>LAI Haloperidol</td>
<td>0.98 (0.74, 1.74)</td>
</tr>
<tr>
<td>LAI Perphenazine</td>
<td>0.39 (0.12, 1.23)</td>
</tr>
<tr>
<td>LAI Flupenthixol</td>
<td>0.39 (0.12, 1.23)</td>
</tr>
<tr>
<td>LAI Olanzapine</td>
<td>0.38 (0.27, 0.54)</td>
</tr>
<tr>
<td>LAI Zuclopenthixol</td>
<td>0.41 (0.33, 0.51)</td>
</tr>
<tr>
<td>Oral Quetiapine</td>
<td>0.41 (0.33, 0.51)</td>
</tr>
<tr>
<td>Oral Perphenazine</td>
<td>0.47 (0.36, 0.63)</td>
</tr>
<tr>
<td>LAI Perphenazine</td>
<td>0.53 (0.44, 0.64)</td>
</tr>
<tr>
<td>Other orals</td>
<td>0.59 (0.45, 0.78)</td>
</tr>
</tbody>
</table>

**Fig. 4:** The adjusted Hazard Ratios of mortality during exposure to antipsychotic monotherapies compared with no use in the prevalent population, including all LAIs and ten most frequently used orals. All treatments except olanzapine LAI, levomepromazine and fluphenazine LAI survived Bonferroni correction (level of significance p < 0.0025).
than exaggerated the observed difference between use versus no use of antipsychotics. Although antipsychotics were compared with time when antipsychotics were not used, the majority of persons did have time periods of antipsychotic use and never-use was rare. Thus, non-use time represents mostly non-treatment periods of users. Lithium use was not considered in the analyses although it may have anti-suicidal effects. The patients using LAs had the highest rate of previous psychiatric hospitalizations, suicide attempts, and substance abuse which co-variates were associates with increased risk of death. This suggests that the superiority of LAs over orals would have been even more robust if residual confounding could have been totally eliminated.

5. Conclusions
Mortality among patients with schizophrenia is over 40% lower during those time periods when the patients use antipsychotics than when they do not. LAL use is associated with an approximately 30% lower risk of death compared with the oral use of the same medication. SG LAs and oral aripiprazole are associated with the lowest mortality.

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Conflict of interest

J. Tiihonen, E. Mittendorfer-Rutz, K. Alexander, E. Jedenius, D. Enkuson, A. Leval, J. Sermon, A. Tanskanen, and H. Taipale were responsible for the study concept and design. E. Mittendorfer-Rutz, K. Alexander, A. Tanskanen, and H. Taipale were responsible for data extraction. M. Majak, J. Mehtälä, and F. Hoti were responsible for statistical analysis. H. Taipale and J. Tiihonen were responsible for drafting the manuscript. All other authors were responsible for critical revision of the manuscript and have accepted the final version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2017.12.010.

References


