20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20)

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Antipsychotics are effective in preventing relapses of schizophrenia, but it is generally believed that their long-term use is harmful for patients' physical well-being. However, there are no long-term studies which have verified this view. This nationwide, register-based cohort study aimed to assess the risk of hospitalization due to physical health problems, as a marker for severe physical morbidity, and the risk of all-cause mortality, as well as of cardiovascular and suicidal death, associated with antipsychotic use in all patients treated for schizophrenia in inpatient care between 1972 and 2014 in Finland (N=62,250), with up to 20 years of follow-up (median: 14.1 years). The use of antipsychotic drugs (i.e., use of any antipsychotic compared with non-use) and the use of specific antipsychotics were investigated, and outcomes were somatic and cardiovascular hospitalization, and all-cause, cardiovascular and suicide death. Hospitalization-based outcomes were analyzed by a within-individual design to eliminate selection bias, comparing use and non-use periods in the same individual by stratified Cox model. Mortality outcomes were assessed by traditional between-individual Cox multivariate models. The adjusted hazard ratios (aHRs) for any somatic hospitalization and cardiovascular hospitalization were 1.00 (95% CI: 0.98-1.03) and 1.00 (95% CI: 0.92-1.07) during use of any antipsychotic compared to non-exposure periods within the same individual. The aHRs were 0.48 (95% CI: 0.46-0.51) for all-cause mortality, 0.62 (95% CI: 0.57-0.67) for cardiovascular mortality, and 0.52 (95% CI: 0.43-0.62) for suicide mortality during use vs. non-use of any antipsychotic. The most beneficial mortality outcome was associated with use of clozapine in terms of all-cause (aHR=0.39, 95% CI: 0.36-0.43), cardiovascular (aHR=0.55, 95% CI: 0.47-0.64) and suicide mortality (aHR=0.21, 95% CI: 0.15-0.29). The cumulative mortality rates during maximum follow-up of 20 years were 46.2% for no antipsychotic use, 25.7% for any antipsychotic use, and 15.6% for clozapine use. These data suggest that long-term antipsychotic use does not increase severe physical morbidity leading to hospitalization, and is associated with substantially decreased mortality, especially among patients treated with clozapine.

Key words: Schizophrenia, antipsychotic treatment, physical morbidity, hospitalization, all-cause mortality, cardiovascular mortality, suicide, clozapine

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Antipsychotics are effective in preventing relapses in schizophrenia, according to both randomized controlled trials (RCTs)[1] and observational studies representing real-world patients with long follow-up periods[2]. However, antipsychotic use is associated with the risk of serious adverse events, such as tardive dyskinesia[3,4]. In addition, adverse effects of antipsychotic drugs on physical health are numerous[5-7]. In short-term treatment, the use of these medications has been associated with weight gain, dyslipidemias, glucose metabolism dysregulation, QTc prolongation and sudden cardiac death[8-11], and many of these adverse effects have been linked with their pharmacological action[9,11,12]. Nevertheless, there is a lack of knowledge about whether these cardiometabolic adverse effects are associated with greater physical morbidity and mortality in long-term use[13,14].

According to a meta-analysis based on studies from various countries, persons with schizophrenia have a 14.5 years shorter average life expectancy compared with the general population[15]. Our recent findings from a large, nationwide cohort study showed that the gap in longevity has remained the same during the last 30 years[16]. This unchanged excess mortality compared with the general population was explained by a simultaneous decrease in suicides and increase in cancer and cardiovascular deaths among persons with schizophrenia.

Persistent premature mortality in schizophrenia might also be attributed to long-term antipsychotic use. However, recent systematic reviews and meta-analyses of short-term placebo-controlled RCTs have found an about 30-50% lower mortality risk in association to antipsychotic use compared with non-use[17,18], although the duration of treatment was not identical for active vs. placebo arms in one of these studies[18], and the statistical power was insufficient to reach a significant difference in the other[17].

Large observational studies have also reported beneficial effects of antipsychotics on all-cause mortality, which has been attributed to more healthy lifestyle behaviors, less psychosis-related cortisol increase, and increased secondary prevention due to engagement with the medical system in antipsychotic-treated patients[19-22].

Data on long-term physical morbidity and mortality associated with antipsychotic use are lacking[1], which would be crucial knowledge for a more in-depth assessment of the long-term risk-benefit ratio of the use of these medications in the treatment of schizophrenia[13]. Thus, we aimed to study the risk of hospitalization due to physical health problems, as a marker for severe physical morbidity, and the risk of all-cause mortality as well as cardiovascular and suicidal death associated with antipsychotic

use in a nationwide cohort of persons with schizophrenia, with up to 20 years of follow-up.

METHODS

Study population

The study population was identified based on the nationwide Hospital Discharge register, which is managed by the National Institute of Health and Welfare. The study cohort included all persons treated in inpatient hospital care due to schizophrenia in Finland during the period 1972-2014[2,23]. Schizophrenia was defined by discharge diagnosis (ICD-10 codes F20 and F25; ICD-9 and ICD-8 codes 295*).

The whole cohort (named as prevalent cohort) included 62,250 persons with schizophrenia, while the incident cohort (first-episode patients) included 8,719 persons who were hospitalized for the first time due to schizophrenia in the period 1996-2014, and who had not used antipsychotic drugs during the year preceding the index hospitalization.

The follow-up started on January 1, 1996 for the prevalent cases, and at the first discharge from inpatient care for the incident cases. The follow-up time ended at death or on December 31, 2015, whichever occurred first.

Exposure

As drug dispensing in the Prescription register data is recorded according to Anatomical Therapeutic Chemical (ATC) classification codes, we derived antipsychotics as class N05A, with exclusion of lithium. The PRE2DUP method was utilized to derive drug use periods, i.e., when drug use started and ended, based on purchase dates, amounts of drugs dispensed and personal drug use patterns[24].

Outcomes

Two inpatient care-based outcomes were defined: somatic hospitalization (all hospitalizations except psychiatric ones, i.e., excluding ICD-10 codes F* as main diagnoses) and cardiovascular hospitalizations (ICD-10 codes I00-I99). Three mortality outcomes were analyzed: all-cause mortality, cardiovascular mortality (ICD-10 codes I00-I99) and suicide death (X60-X84). Follow-up for mortality in hospital care was censored after the first seven days, due to lack of drug data during hospital care. Sensitivity analyses for all-cause mortality were conducted without this censoring.

Statistical analyses

Hospitalization-based outcomes (somatic and cardiovascular hospitalization) were analyzed by a within-individual design, which is suitable for recurrent events. A stratified Cox proportional hazard regression model[25] was utilized, in which each individual formed his/her own stratum, and the risk of outcome was compared between exposure and non-exposure periods for each person. The follow-up time for each individual was reset to zero after each outcome event. In within-individual analyses, all time invariant covariates (such as genetics and gender) are controlled for in the design, and only time-varying covariates are adjusted for. These covariates were the temporal order of exposures, time since cohort entry, and use of other psychotropics (antidepressants, benzodiazepines and related drugs, lithium and other mood stabilizers).

Mortality outcomes were analyzed by traditional multivariate-adjusted Cox regression models. These analyses were adjusted for gender, age at cohort entry, year of cohort entry, time since diagnosis, number of prior psychiatric hospitalizations, temporal order of exposure to antipsychotics, other medication use, non-adherence, prior use of long-acting injectable (LAI) antipsychotics, prior suicide attempt, substance abuse and physical comorbidities.

Sensitivity analyses were conducted among incident patients, and by excluding the first ten years of follow-up from the analyses for each person (long-term survivors). Long-term survivors were analyzed to explore longer-term effects on all-cause mortality after patients had passed the highest risk time for suicide[26]. In addition, time-dependent Kaplan-Meier curves for all-cause mortality were drafted to describe the mortality hazard of antipsychotic use versus non-use, and for the ten most commonly used antipsychotics.

Monotherapy periods of specific antipsychotics were analyzed, with all periods including more than one antipsychotic coded as "polytherapy". Additional analyses were conducted with "any therapy" models, where use of a specific drug was assessed as "yes" or "no", independent of concomitant use of other antipsychotics (but adjusted for this variable). The threshold of significance for p values was corrected for multiple comparisons using the Benjamini-Hochberg false discovery rate method.

To assess cumulative exposure, sensitivity analyses on cumulative proportion of days exposed to antipsychotics during outpatient observation time were conducted in a nested case-control design for incident patients. Days of exposure to antipsychotic drugs were divided by outpatient observation time, resulting in categorization as 0% (full non-adherence), >0 to <80% (partial non-adherence) and ≥80% (adherence). Outcomes were all-cause and cardiovascular mortality.

The research project was approved by the Ethics Committee of the Finnish National Institute for Health and Welfare. Further permissions were granted by pertinent institutional authorities at the Institute, the Social Insurance Institution of Finland, and Statistics Finland.

RESULTS

At the start of follow-up, the median age was 45.6 years (interquartile range, IQR=34.6-57.9; mean=46.8) in the prevalent cohort (N=62,250), and 36.2 years (IQR=26.2-52.3, mean=41.2)

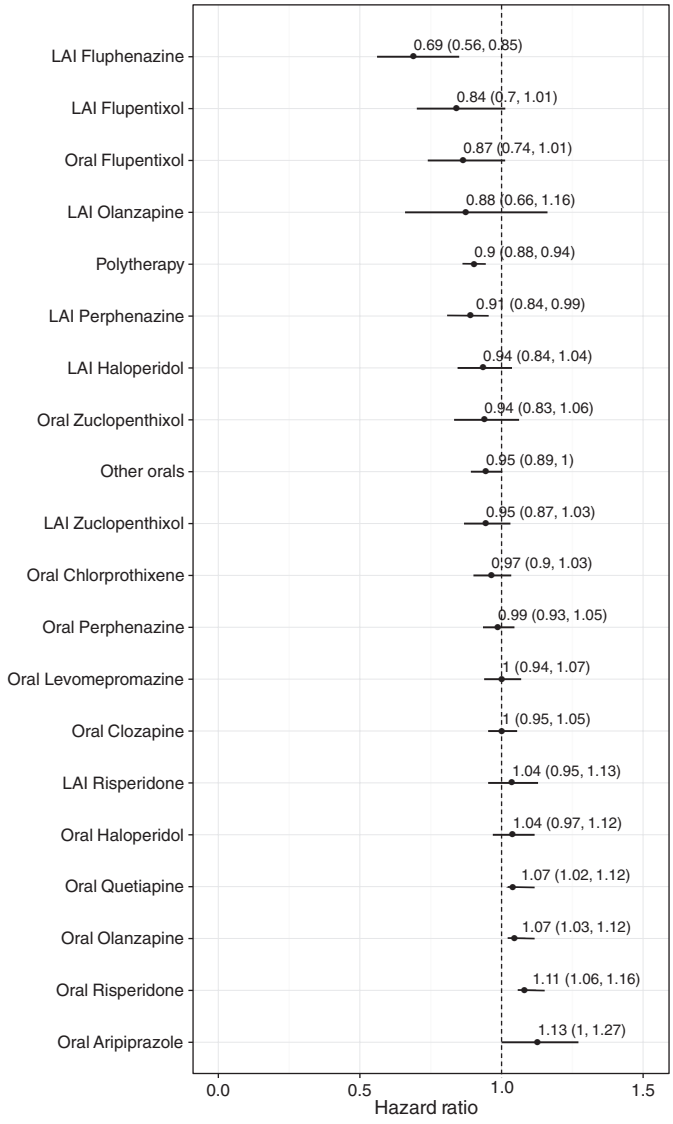

Figure 1 Risk of somatic hospitalization during monotherapy with specific antipsychotics compared with no use of antipsychotics in the prevalent cohort (adjusted hazard ratios with 95% CIs). LAI – long-acting injectable

in the incident cohort (N=8,719). The proportion of males was 50.2% in the prevalent cohort and 56.2% in the incident cohort. The prevalence of comorbid conditions at baseline in the prevalent cohort was as follows: 4.0% for alcohol or substance abuse, 4.8% for cardiovascular disease, 5.1% for diabetes, 0.2% for liver disease, and 0.8% for renal disease.

The median follow-up time was 14.1 years (IQR=6.9-20.0) for the prevalent cohort and 10.1 years (IQR=5.0-14.3) for the incident cohort. During the follow-up, 13,889 (22.3%) persons of the prevalent cohort died, and 42,271 persons (67.9%) experienced somatic hospitalization. The corresponding figures for the incident cohort were 1,160 (13.3%) and 4,488 (51.5%). When censoring to >7 days hospitalizations, the median follow-up time was 13.2 years (IQR 6.2-19.3) in the prevalent cohort, and 9.4 years (IQR 4.5-13.6) in the incident cohort.

Antipsychotic use in monotherapy was not associated with an increased risk of somatic hospitalizations (adjusted hazard ratio, aHR=1.00, 95% CI: 0.98-1.03) compared with non-exposure periods within the same individual (153,149 somatic hospitalizations per 579,306 person-years of antipsychotic use vs. 49,717 somatic hospitalizations per 188,107 person-years of non-use).

Among specific antipsychotics, LAI fluphenazine was associated with the highest decrease of risk (HR=0.69, 95% CI: 0.56-0.85), whereas quetiapine, olanzapine, risperidone and aripiprazole were associated with a slightly increased risk of somatic hospitalizations. Point estimates for the majority of other antipsychotics were around 1.0, with CIs crossing 1.0 (Figure 1).

Mainly similar results were observed for specific antipsychotics used in any therapy (with or without concomitant other antipsychotics), and when within-individual monotherapy model was additionally adjusted for use of somatic co-medications.

Antipsychotic use was not associated with an increased risk of cardiovascular hospitalization (aHR=1.00, 95% CI: 0.92-1.07) compared with non-use periods within the same individual. LAI fluphenazine in monotherapy was associated with a significantly

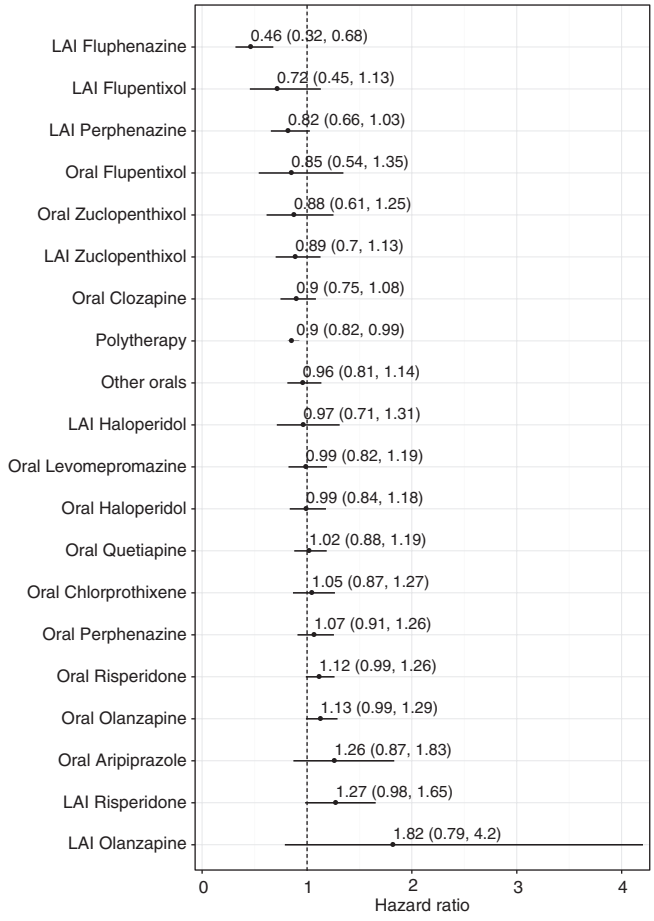

Figure 2 Risk of cardiovascular hospitalization during monotherapy with specific antipsychotics compared with no use of antipsychotics in the prevalent cohort (adjusted hazard ratios with 95% CIs). LAI – long-acting injectable

decreased risk of cardiovascular hospitalization (aHR=0.46, 95% CI: 0.32-0.68) (Figure 2).

All-cause mortality was significantly lower in patients using any antipsychotic compared with those using none (Figure 3). In Kaplan-Meier analyses, the cumulative mortality rates during follow-up up to 20 years were 46.2% for non-use, 25.7% for any antipsychotic use, and 15.6% for clozapine use (p<0.0001). The aHR for all-cause mortality was 0.48 (95% CI: 0.46-0.51) during antipsychotic use compared with non-use in the prevalent cohort (8,264 deaths per 577,417 person-years of antipsychotic use vs. 5,635 deaths per 187,773 person-years of non-use). The corresponding figure in the incident cohort was aHR=0.64 (95% CI: 0.55-0.75) (540 deaths per 55,069 person-years of antipsychotic use vs. 620 deaths per 25,634 person-years of non-use).

Most of the specific antipsychotics in monotherapy were associated with a lower risk of death (Figure 4), with similar results in any therapy analyses.

Cardiovascular mortality was also significantly lower (aHR= 0.62, 95% CI: 0.57-0.67) during any antipsychotic use compared with non-use in the prevalent cohort. The corresponding figure in the incident cohort was aHR=0.83 (95% CI: 0.63-1.09). No specific antipsychotic was associated with an increased risk. Instead, several antipsychotics were associated with a significantly reduced cardiovascular death risk compared with no use (aHR=0.14, 95% CI: 0.02-1.01 for LAI olanzapine; aHR=0.24, 95% CI: 0.11-0.54 for oral flupentixol) (Figure 5).

Suicide mortality was significantly lower (aHR=0.52, 95% CI: 0.43-0.62) during antipsychotic use compared with non-use in the prevalent cohort. The corresponding figure in the incident cohort was aHR=0.50 (95% CI: 0.33-0.74). Several antipsychotics were associated with a reduced suicide mortality (Figure 6).

Overall, the most beneficial mortality outcome was associated with clozapine, considering all-cause (aHR=0.39, 95% CI: 0.36-0.43), cardiovascular (aHR=0.55, 95% CI: 0.47-0.64) and suicide mortality (aHR=0.21, 95% CI: 0.15-0.29). Clozapine was used by 14,350 (23.1%) of persons at some point during the follow-up. The weakest mortality outcome was associated with levomepromazine, considering all-cause (aHR=0.82, 95% CI: 0.71-0.93), cardiovascular (aHR=1.02, 95% CI: 0.84-1.23) and suicide mortality (aHR=0.81, 95% CI: 0.52-1.26).

The results of the sensitivity analyses among first-episode patients were consistent with primary analyses (clozapine monotherapy: aHR=0.42, 95% CI: 0.30-0.59 for all-cause mortality, and aHR=0.46, 95% CI: 0.19-1.09 for cardiovascular mortality). In the comparison between any LAI versus an equivalent oral antipsychotic, they were associated with similar mortality risk (aHR=1.00, 95% CI: 0.93-1.07). Analyses of all-cause mortality in the prevalent cohort without censoring to >7 days hospitalizations yielded similar results as with censoring.

In sensitivity analysis excluding the first 10 years of follow-up, the most favorable outcome for all-cause mortality was observed with LAI olanzapine (aHR=0.13, 95% CI: 0.03-0.53) and oral flupentixol (aHR=0.36, 95% CI: 0.16-0.81), whereas clozapine ranked as 7th among the 19 most frequently used antipsychotics (aHR=0.47, 95% CI: 0.41-0.54).

The results of sensitivity analyses with a nested case-control design on associations between cumulative antipsychotic exposure and all-cause and cardiovascular mortality were also consistent with the primary analyses. Compared with non-use of antipsychotics, use for ≥80% of outpatient observation time was associated with a decreased risk of all-cause mortality (adjusted odds ratio, aOR=0.73, 95% CI: 0.60-0.88). For cardiovascular mortality, antipsychotic use was also associated with a decreased risk, but confidence intervals were wide, resulting in non-significant findings (aOR=0.80, 95% CI: 0.57-1.12). Results for clozapine use were similar to those for any antipsychotic use, concerning both all-cause mortality (aOR=0.61, 95% CI: 0.44-0.86) and cardiovascular mortality (aOR=0.54, 95% CI: 0.21-1.39).

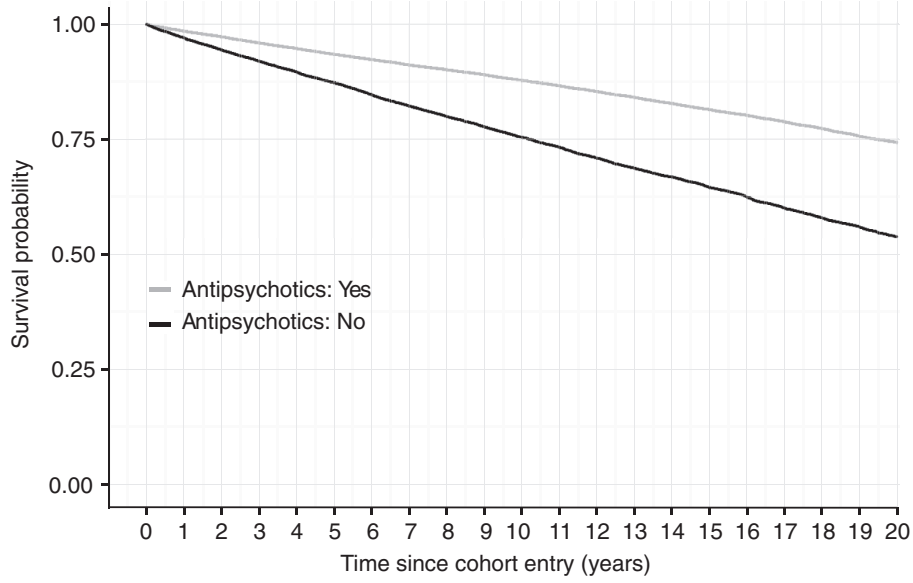

Figure 3 All-cause mortality in patients using any antipsychotic versus those who used none in the prevalent cohort

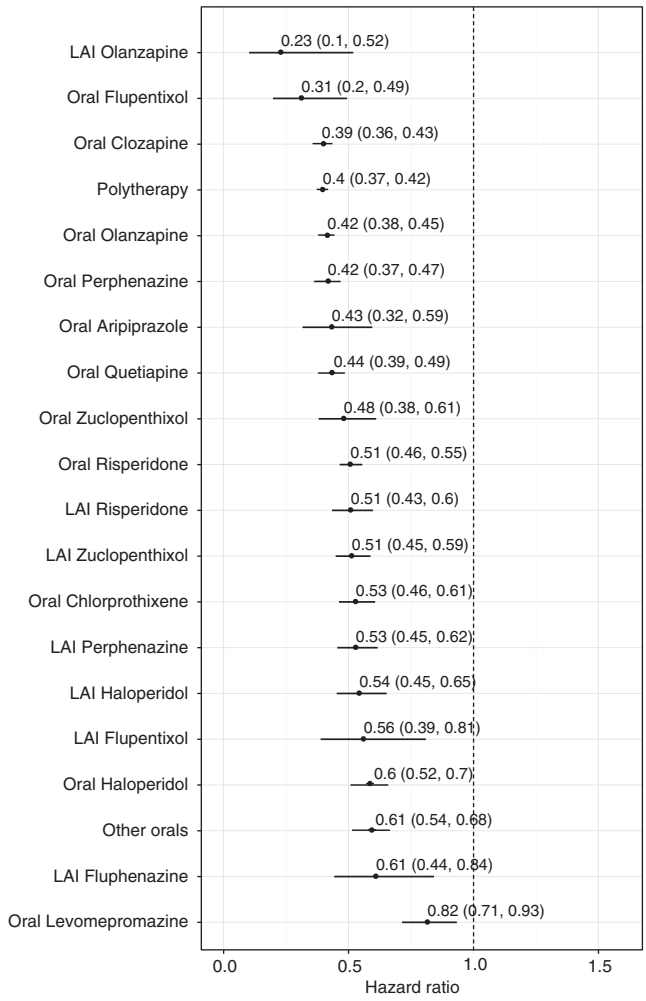

Figure 4 All-cause mortality in patients receiving monotherapy with specific antipsychotics compared to those who received none in the prevalent cohort with censoring to >7 days hospitalizations (adjusted hazard ratios with 95% CIs). LAI – long-acting injectable

DISCUSSION

In this non-randomized, observational, nationwide sample with up to 20 years of follow-up (median 14.1 years), we found that antipsychotic use was not associated with an increased risk of hospitalization due to somatic or cardiovascular reasons in patients with schizophrenia. Furthermore, antipsychotic use was associated with a decreased risk of all-cause, cardiovascular and suicide mortality, also in terms of cumulative antipsychotic exposure. Among specific antipsychotics, clozapine was associated with the most beneficial outcome concerning reduced mortality.

Our results on the association between antipsychotic use and mortality are consistent with previous observational studies[19-22,27]. However, the present investigation uniquely adds to the literature with the largest cohort ever, allowing meaningful analyses regarding specific antipsychotics, plus truly long-term follow-up of up to 20 years compared with 5-11 years in previous studies. Thus, we were able to assess longer-term outcomes, which is important due to the life-long duration of schizophrenia and the occurrence of adverse events as a function of long-term cumulative exposure.

Regarding physical morbidity, periods of antipsychotic use were not associated with an increased risk of somatic or cardiovascular hospitalizations. These findings on long-term outcomes may appear inconsistent with the adverse effects of short-term antipsychotic use, including weight gain and obesity, impaired glucose tolerance, dyslipidemias and cardiovascular events, which are all intermediate risk factors for cardiovascular morbidity and mortality[9,11,12,14]. An explanation for this disconnect is likely to be the improved control of psychiatric symptoms associated with antipsychotic use, which in turn may lead to improved adherence to healthy lifestyle behaviors and utilization of health care services for physical illnesses[13].

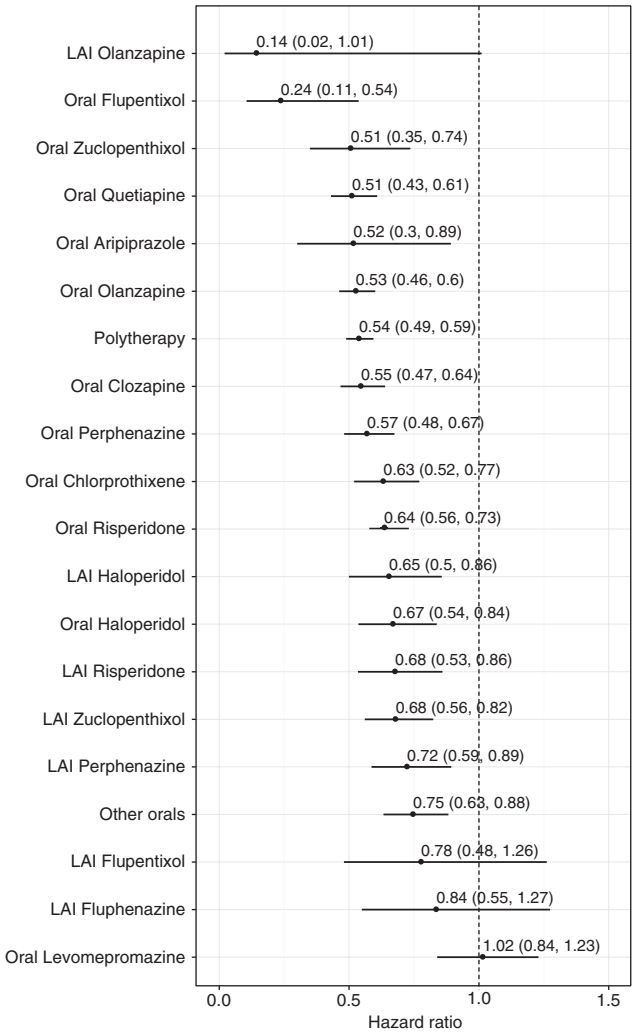

Figure 5 Cardiovascular mortality in patients receiving monotherapy with specific antipsychotics compared to those who received none in the prevalent cohort with censoring to >7 days hospitalizations (adjusted hazard ratios with 95% CIs). LAI – long-acting injectable

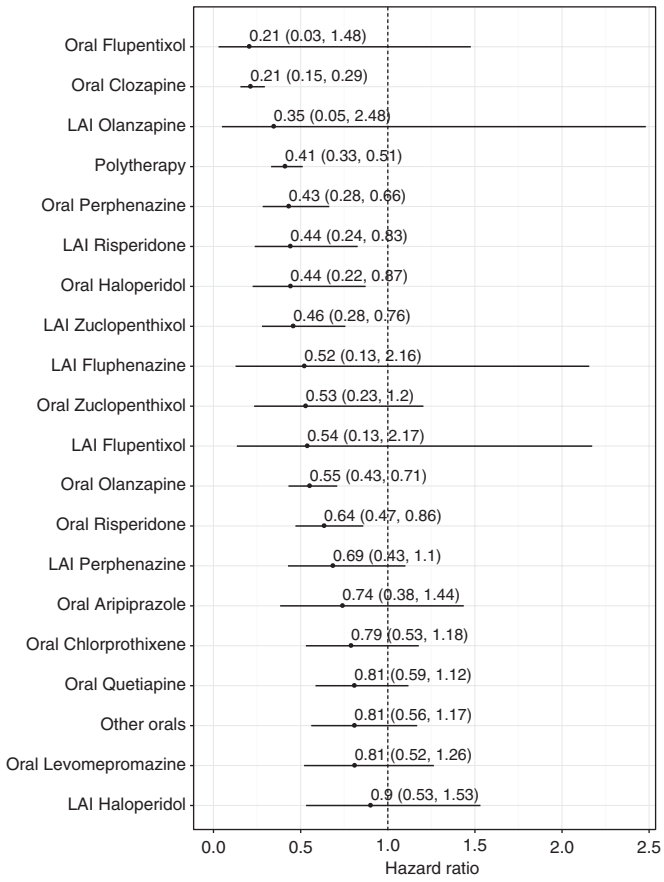

Figure 6 Suicide mortality in patients receiving monotherapy with specific antipsychotics compared to those who received none in the prevalent cohort with censoring to >7 days hospitalizations (adjusted hazard ratios with 95% CIs). LAI – long-acting injectable

Persons with schizophrenia have a greater prevalence of sedentary lifestyle, obesity and smoking[6,28,29], are less likely to receive adequate pharmacotherapy for hypertension and dyslipidemias[30,31], and are seldom tested for glucose and lipid alterations[32,33]. This problematic general reduction in adequate secondary prevention of cardiovascular morbidity and mortality is likely aggravated in individuals with schizophrenia not taking antipsychotics.

There are several other possible mechanisms explaining the decreased mortality in patients receiving antipsychotic treatment. Antipsychotics reduce symptoms of schizophrenia, and this may be a major factor for decreased suicide mortality[20]. Relief of stress may also have a beneficial effect on cardiovascular mortality. Smoking and high blood pressure are among the most important risk factors for cardiovascular death[34], and antipsychotics, especially clozapine, decrease blood pressure and possibly also the rate of smoking[35,36].

The results of our study are consistent with previous results from Sweden[21]. However, some differences in the comparative effectiveness of specific antipsychotics emerged. In the Swedish study, LAIs were associated with a 33% lower risk of all-cause mortality compared with equivalent oral antipsychotics[21], while in the current study no significant difference between LAIs and oral antipsychotics was observed. The superiority of LAIs in Sweden may be related to the fact that those preparations were used more frequently (29% of all antipsychotic use person-years) during the observation period in that country (2006-2013)[21], compared to this study in Finland (8.5% of antipsychotic use person-years in the period 1996-2015).

We found that clozapine was associated with the lowest mortality, in line with the meta-analysis by Vermeulen et al[37], which reported that continuous clozapine treatment is associated with an about 40% lower all-cause mortality compared to other antipsychotics. Clozapine is recommended for use after two other antipsychotics have been ineffective[38] and, therefore, is generally initiated later in the illness course than other antipsychotics. Since mortality may be particularly high in the early phase of the illness[39], the later use of clozapine could introduce a survival bias. Therefore, we conducted sensitivity analyses by excluding the first ten years of follow-up. In these analyses, clozapine was indeed associated with a slightly lower comparative effectiveness, ranking as 7th among the 19 most frequently used antipsychotics in monotherapy. This finding suggests that survival bias related to early phase mortality may affect the rank order of antipsychotics to some extent.

To our knowledge, this is the largest cohort with the longest follow-up to study morbidity and mortality during antipsychotic treatment in people with schizophrenia or any diagnosis. The results may be particularly generalizable to countries with a state-funded health care system, where antipsychotics are provided for patients with no or very small co-payments. Antipsychotic use was modelled with the PRE2DUP method[24], which produces reliable estimates of drug exposure and performs better than other previously used modelling methods for register-based data[40].

Hospitalization-based outcomes were analyzed by within-individual analyses. All time-invariant factors are controlled for in this design, which therefore is superior to other analyses in adjusting for fixed and even unmeasured characteristics such as diet, exercise and genetic factors. The underlying severity of disease is also controlled for in this design, which is an advantage over traditional observational studies, and the impact of co-medications was adjusted for.

One theoretical source of bias is that a patient may experience a side effect and discontinue medication, be hospitalized a few days or weeks later, and counted as a non-user of antipsychotic drugs. However, in Finland, each prescription dispensing lasts typically 90 days. The exact timing of discontinuation of use is not known, and drug use modelling assumes that all medications dispensed are used. In addition, the utilized modelling method adds some days of extra duration after the calculated antipsychotic drug use has ended, in order to ensure that the end of drug use is correctly assigned if some down-titration happens after long drug use. These design features ensure that rapid antipsychotic discontinuations provoked by adverse effects are assigned to the antipsychotic exposure instead of non-exposure period, and that no major misclassification of "past users" occurs.

Mortality analyses were traditional between-individual models and were adjusted for comorbid conditions associated with survival. The analyses were also adjusted for time-dependent use of other medications, which aimed at better control for emergence and progression of the comorbid conditions during long follow-up. Temporal order of antipsychotics was adjusted for in all analysis, by taking into account that clozapine is initiated later. Sensitivity analyses aimed at analyzing possible sources of bias, and the results of these analyses did not change the overall interpretation of data.

As in all observational studies, residual confounding may exist, especially in between-individual analyses. We lacked information on important lifestyle behaviors, such as smoking and diet. Somatic comorbidities were based only on diagnoses in hospital care and were, therefore, likely under-reported. The impact of this potential bias was reduced by updating data on comorbid conditions in a time-dependent fashion in the between-individual analyses. Survival bias related to prevalent cases was reduced by conducting analyses separately among incident cases, and the results were similar, although the sample size and number of deaths was reduced, which limited statistical power.

In conclusion, in this nationwide observational study, long-term antipsychotic use was not associated with increased severe physical morbidity among persons with schizophrenia when comparing exposure and non-exposure periods in the same person. In addition, compared to no antipsychotic use, long-term antipsychotic use was associated with substantially lower all-cause, cardiovascular and suicide mortality in people with schizophrenia. These results indicate that excess mortality in schizophrenia may not be attributable to antipsychotics, but at least partially and to a relevant degree to non-use of antipsychotics.

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