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Comparative Effectiveness of Antipsychotic Drugs for Rehospitalization in Schizophrenia—A Nationwide Study With 20-Year Follow-up

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Very little is known about the comparative long-term effectiveness of novel antipsychotics in relapse prevention, especially in first-episode schizophrenia. Nationwide data from Finnish health care registers were gathered prospectively for all persons with periods of inpatient care due to schizophrenia in Finland during 1972–2014. Altogether 62 250 persons were included in the prevalent cohort, and 8719 in the incident (first-episode schizophrenia) cohort. The follow-up for antipsychotic use started at 1996 for the prevalent cohort, and at the first discharge from inpatient care for the incident cases. Within-individual Cox regression models for risk of psychiatric and all-cause hospitalization were constructed to compare risk during antipsychotic use and no use using individual as his/her own control to eliminate selection bias. With follow-up time up to 20 years (median = 14.1, interquartile range = 6.9–20.0), 59% of the prevalent cohort were readmitted to psychiatric inpatient care. Olanzapine long-acting injection (LAI; adjusted hazard ratio = 0.46, 95% confidence interval = 0.36–0.61), clozapine (0.51, 0.49–0.53), and paliperidone LAI (0.51, 0.40–0.66) were associated with the lowest risk of psychiatric rehospitalization in the prevalent cohort. Among first-episode patients, the lowest risks were observed for flupentixol LAI (0.24, 0.12–0.49), olanzapine LAI (0.26, 0.16–0.44), and perphenazine LAI (0.39, 0.31–0.50). Clozapine and LAIs were associated with the lowest risk of all-cause hospitalization in both cohorts. Clozapine and LAIs are the most effective treatments in preventing psychiatric and all-cause hospitalization among chronic and first-episode patients with schizophrenia.

Key words: treatment/hospitalization/nationwide cohort

Introduction

Better treatment choices to improve treatment outcomes for schizophrenia have been explored as besides personal suffering also due to high health care costs associated with the disease.[1] Hospitalizations may be caused by treatment relapses leading to psychiatric inpatient care, or adverse effects associated with antipsychotic drug use leading to nonpsychiatric care. Findings on comparative effectiveness of antipsychotic drugs from randomized controlled trials (RCTs)[2] offer some guidance for clinicians. However, more focus has been paid to the issue whether participants of RCTs are representative of real-life patients with schizophrenia or a highly selected subgroup.[3] In addition, RCT participants often receive better care during the trial than what is possible to offer in usual care, and persons who are nonadherent to their medication are unlikely to volunteer for clinical trials.

The most effective treatment may also depend on whether a patient is newly diagnosed with schizophrenia or has a long history with the disease. Furthermore, first-time users of antipsychotic drugs may differ from those who have used these drugs for a long time, as first-time users are more likely to experience even serious adverse effects than long term users tolerating the drug. As pointed out by Vanasse et al,[4] this survival bias can be avoided by using new user design for the incident cases. As incidence of schizophrenia is rather low, around 0.3–0.5 new cases per 1000 persons and has a somewhat decreasing trend[5,6] the sample size for the incident patients often is limited which may lead to either lack of statistical power or focus on only the most commonly used antipsychotics. Previous observational studies among the incident schizophrenia patients have demonstrated superiority of clozapine over other antipsychotics.[4,7–9] However, not all studies have differentiated between oral and long acting injection forms[4] although administration route may have large impact on treatment outcomes.[9] Also, the number of the patients in all previous studies has been too low and the length of follow-up too short to allow meaningful comparison

between all commonly used medications. Thus, more research is needed on comparative effectiveness of antipsychotic drugs in first episode schizophrenia.

As duration of RCTs often is very limited (from only 4 weeks until up to 1 year),[2] together with the fact that schizophrenia is a life-long disease, more real-world data are needed on comparative effectiveness of antipsychotics in long-term treatment of schizophrenia. Observational studies utilizing large nationwide registers may overcome issues related to selected patients in RCTs (as all patients can be included and selection bias avoided) and possibility to follow-up patients is practically limited only by duration of data collection in the registers. Previous observational studies had limited follow-up time from 5 years to up to 11 years.[4,7–11] The objective of this study was to investigate the risk of all-cause and psychiatric hospitalization associated with antipsychotic drugs in nationwide cohort of persons with schizophrenia with up to 20-year follow-up. Subgroup analyses of the incident schizophrenia cases with no previous antipsychotic use were conducted.

Methods

Study Population

Study cohort consisted of all persons treated in inpatient hospital care due to schizophrenia during 1972–2014 in Finland. They were identified from Hospital Discharge register maintained by the National Institute of Health and Welfare. Other registers utilized were Prescription register (maintained by Social Insurance Institution, 1995–2015) and data on dates of death (1972–2015).

Hospital Discharge register includes all inpatient hospital stays in Finland, recorded for all residents. Schizophrenia was defined as discharge diagnoses codes (ICD-10) F20, F25; and (ICD-9 and ICD-8) 295*. During 1972–2014, altogether 81 043 persons were hospitalized due to schizophrenia. Persons with diagnoses of dementia ($N = 1166$) before or at the same time as schizophrenia were excluded, resulting in 79 877 persons. Persons who died during the first hospitalization ($N = 2599$) and who died before January 1, 1996 ($N = 15\,028$) were excluded. The follow-up started at 1996 for the prevalent cohort, and at the first discharge from inpatient care for the incident cases. The final prevalent cohort included 62 250 persons with schizophrenia. The follow-up time ended at death or December 31, 2015 whichever occurred first.

In addition, the incident cohort was defined as persons hospitalized for the first time due to schizophrenia during 1996–2014 ($N = 23\,499$) and who had not used antipsychotic drugs during 1 year preceding the index hospitalization ($N = 8719$ the incident cases). For the incident cohort, cohort entry was defined as their first hospitalization due to schizophrenia, and the follow-up time was from diagnosis until end of year 2015 or death, as for the prevalent cohort.

Exposure

Antipsychotic use was derived from Prescription register based on Anatomical Therapeutic Chemical (ATC) classification code N05A excluding lithium.[12] Detailed information on ATC codes and defined daily doses (DDDs) is given by the WHO Collaborating Centre for Drug Statistics Methodology.[12] Antipsychotic drug dispensings were modeled with PRE2DUP method to drug use periods which describe when drug use started and ended.[13] The method takes into account on regularity of dispensings, hospitalizations, and possible stockpiling of drugs. The modeling was conducted based on drug formulation (indicated by package information) to separate antipsychotic substances as oral and long-acting injections (LAI). Drug substances were grouped as first-generation and second-generation antipsychotics as listed in supplementary table 1.

Outcomes

The main outcome measure was psychiatric rehospitalization, defined as ICD-10 codes F20–29 as main diagnoses. As antipsychotic use could also lead to other hospitalizations than psychiatric (especially due to adverse effects) the secondary outcome measure was all-cause hospitalization.

Covariates

In within-individual models, person acted as his/her own control. Thus, within-individual models were adjusted only for time-dependent covariates which were the order of exposures, time since cohort entry, use of other psychotropic drugs (antidepressants, benzodiazepines, lithium, mood stabilizers, sedatives), and concomitant use of multiple antipsychotics, ie, antipsychotic polypharmacy.

The traditional Cox models were adjusted for gender, age at cohort entry, year of cohort entry, time since diagnosis, number of prior psychiatric hospitalizations, comorbidities, and drug use. The exact definitions are provided in the supplementary table 2.

Statistical Analyses

Both outcomes (psychiatric and all-cause hospitalization) were treated as recurrent events and analyzed with a stratified Cox proportional hazard regression models.[9] In these within-individual models, each individual formed his or her own stratum, and follow-up time was reset to zero after each outcome event. Persons with both variation in exposure during the follow-up and who experienced an outcome event contributed to within-individual analysis. The main analysis compared specific antipsychotic use in monotherapy to no use of antipsychotics. In these analysis, concurrent use of multiple antipsychotic drugs was recorded to a separate category of

"polytherapy." Sensitivity analyses were conducted by comparing specific antipsychotic use in monotherapy to most commonly used antipsychotic, oral olanzapine, and specific antipsychotic use (including also polytherapy periods) to nonuse of that particular antipsychotic. All analyses were conducted in the prevalent cohort (including all included schizophrenia cases) and in the incident cohort which included first-episode cases. Traditional multivariate-adjusted Cox regression was utilized for between-individual models. These models were adjusted for covariates provided in supplementary table 2.

The research project was approved by the Ethics Committee of the Finnish National Institute for Health and Welfare (dated December 4, 2013, 8/2013). Further permissions were granted by pertinent institutional authorities at the Finnish National Institute for Health and Welfare (permission THL/1466/6.02.00/2013), The Social Insurance Institution of Finland (34/522/2013), and Statistics Finland (TK53-305–13).

Results

The follow-up time in this study was up to 20 years, with median time 14.1 years (interquartile range = 6.9–20.0 years) in the prevalent cohort, and 10.1 years (interquartile range = 5.0–14.3) in the incident cohort (table 1). During the follow-up, 58.8% ($N = 36\,631$) of the prevalent cohort and 57.9% ($N = 5045$) of the incident cohort were readmitted to psychiatric inpatient care. Similar numbers for all-cause hospitalization were 86.2% ($N = 53\,633$) of the prevalent cohort and 80.0% ($N = 6971$) of the incident cohort. Median doses of specific antipsychotics used in the prevalent and incident cohorts are described in supplementary table 3.

Table 1. Baseline Characteristics of the Prevalent and the Incident Cohorts and Hospitalizations During the Follow-up

	The Prevalent Cohort, $N = 62\,250$, % (N)[a]	The Incident Cohort, $N = 8719$, % (N)[a]
Age		
≤24	8.6 (5368)	21.2 (1844)
25–34	17.3 (10 748)	26.3 (2297)
35–44	22.5 (13 996)	16.3 (1417)
45–54	22.1 (13 767)	14.5 (1266)
55–64	14.2 (8833)	8.8 (763)
≥65	15.3 (9538)	13.0 (1132)
Median age (IQR)	45.6 (34.6–57.9)	36.2 (26.2–52.3)
Male gender	50.2 (31 257)	56.2 (4898)
Number of all-cause hospitalizations		
0	13.8 (8617)	20.0 (1748)
1	12.8 (7948)	16.6 (1443)
2–4	27.6 (17 194)	29.9 (2603)
5–8	20.0 (12 423)	17.4 (1520)
≥9	25.8 (16 068)	16.1 (1405)
Median number of all-cause hospitalizations per person (IQR)	4 (1–9)	3 (1–6)
Number of psychiatric hospitalizations		
0	41.2 (25 619)	42.1 (3674)
1	16.4 (10 233)	18.5 (1615)
2–4	21.7 (13 490)	22.7 (1980)
5–8	10.1 (6273)	9.2 (805)
≥9	10.7 (6635)	7.4 (645)
Median number of psychiatric hospitalizations per person (IQR)	1 (0–4)	1 (0–3)
Median follow-up time, years	14.1 (6.9–20.0)	10.1 (5.0–14.3)

Note: IQR, interquartile range.
[a]If not otherwise indicated.

Oral Vs LAI Comparisons

LAI use was associated with lower risk of psychiatric rehospitalization especially among the incident cohort. Risk of psychiatric hospitalization was lower during LAI use (first generation LAIs = 0.46, 95% CI = 0.40–0.54; second generation LAIs = 0.45, 95% CI = 0.39–0.52) than during oral antipsychotic use (first generation orals HR = 0.67, 95% CI = 0.60–0.74; second generation orals HR = 0.57, 95% CI = 0.53–0.61) in the incident cohort whereas in the prevalent cohort, differences between these drug classes were less pronounced (HRs from 0.57 to 0.65).

Risk of all-cause hospitalization was somewhat lower during LAI use (first generation LAIs HR = 0.69, 95% CI = 0.66–0.71; second generation LAIs HR = 0.70, 95% CI = 0.67–0.74) than during oral antipsychotic use in the prevalent cohort (first generation orals = 0.73, 95% CI = 0.71–0.75; second generation orals HR = 0.78, 95% CI = 0.76–0.79). In the incident cohort, LAI use was also associated with lower risk of all-cause hospitalization (first generation LAIs HR = 0.58, 95% CI = 0.51–0.66; second generation LAIs HR = 0.56, 95% CI = 0.50–0.63) than oral antipsychotic use (first generation orals HR = 0.80, 95% CI = 0.74–0.87; second generation orals HR = 0.69, 95% CI = 0.66–0.73).

Specific Antipsychotics

Of specific antipsychotics used in monotherapy, olanzapine LAI (HR = 0.46, 95% CI = 0.36–0.61), clozapine (HR = 0.51, 95% CI = 0.49–0.53), and paliperidone LAI (HR = 0.51, 95% CI = 0.40–0.66) were associated with the lowest risk of psychiatric rehospitalization compared with no antipsychotic use in the prevalent cohort (figure 1). In the incident cohort, the lowest risks were observed for flupentixol LAI (0.24, 0.12–0.49), olanzapine LAI (0.26, 0.16–0.44), and perphenazine LAI (0.39, 0.31–0.50) (figure 2). Incidence rates for psychiatric

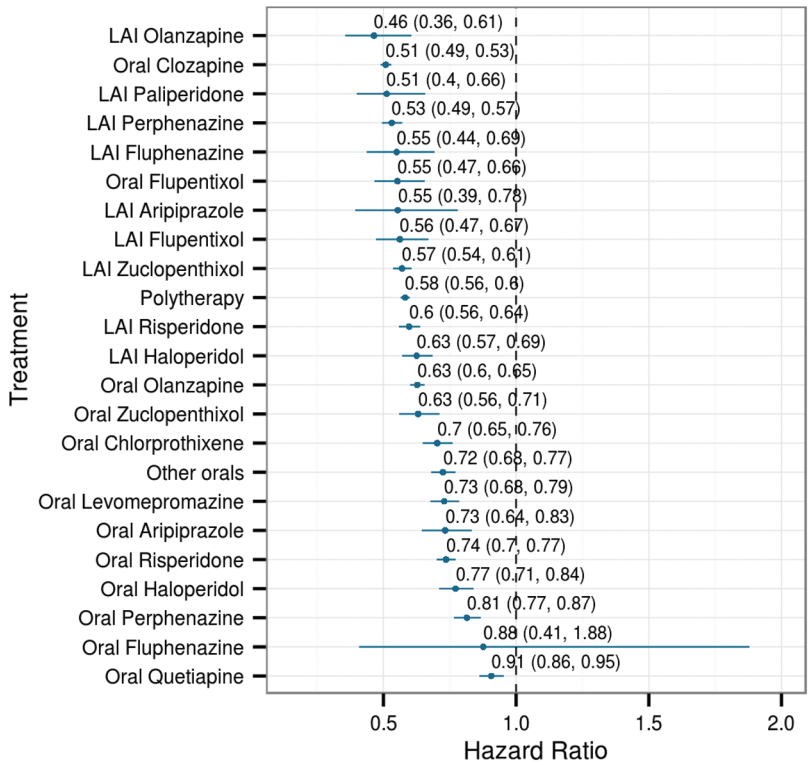

Fig. 1. Risk of psychiatric rehospitalization in monotherapy of specific antipsychotics in comparison to no use of antipsychotic in the prevalent cohort, within-individual model.

hospitalization are provided in supplementary table 1. The same antipsychotics were associated with the lowest psychiatric rehospitalization risks when compared with oral olanzapine (supplementary figures 1 and 2), and when compared with no use of specific antipsychotic (allowing also polytherapy; supplementary figures 3 and 4). In sensitivity analyses with traditional Cox models in the prevalent cohort, the HRs for many LAIs did not reach significance and the lowest risk of psychiatric rehospitalization compared with no antipsychotic use was found for oral flupentixol, fluphenazine, and clozapine (supplementary figure 5).

For all-cause hospitalization, almost the same antipsychotics were associated with lowest risk as for psychiatric hospitalization. In the prevalent cohort, olanzapine LAI (HR = 0.53, 95% CI = 0.42–0.66), clozapine (HR = 0.60, 95% CI = 0.58–0.61), and fluphenazine LAI (HR = 0.60, 95% CI = 0.51–0.69) were associated with the lowest risk of all-cause hospitalization in monotherapy (figure 3). In the incident cohort, the lowest risks were observed for olanzapine LAI (HR = 0.34, 95% CI = 0.22–0.53), flupentixol LAI (HR = 0.39, 95% CI = 0.21–0.72) and clozapine (HR = 0.51, 95% CI = 0.47–0.56), followed by perphenazine LAI (HR = 0.52, 95% CI = 0.43–0.64) (figure 4). Incidence rates for all-cause hospitalization are provided in supplementary table 4. In traditional between-subject model, HRs for antipsychotics associated with the lowest all-cause hospitalization risk attenuated but the rank order of antipsychotics remained almost the same in the prevalent population (supplementary figure 6).

The risk of psychiatric rehospitalization was also compared within each specific antipsychotic, LAI use, and no use were compared with oral use as the reference (supplementary figure 7). This comparison demonstrates that not all LAIs are superior to oral formulations of the same antipsychotic. LAIs associated with lower risk of psychiatric rehospitalization compared with the corresponding oral were risperidone LAI (HR = 0.79), perphenazine LAI (HR = 0.81), olanzapine LAI (HR = 0.83), and haloperidol LAI (HR = 0.83), whereas no significant difference was found for zuclopenthixol LAI, fluphenazine LAI, flupentixol LAI, and aripiprazole LAI.

Discussion

In this study, we found that LAIs were associated with lower risk of psychiatric and all-cause hospitalization than oral antipsychotics. This was seen both in the prevalent and the incident cohorts. Of specific antipsychotics, olanzapine LAI and clozapine were associated with the lowest risk of hospitalization in all analyses. With up to 20-year follow-up time and large, unselected cohort of real-life schizophrenia patients, this study provides strong evidence on effectiveness of LAIs and clozapine over other antipsychotics. Further, within-individual analyses avoid selection of users as these analyses compared the

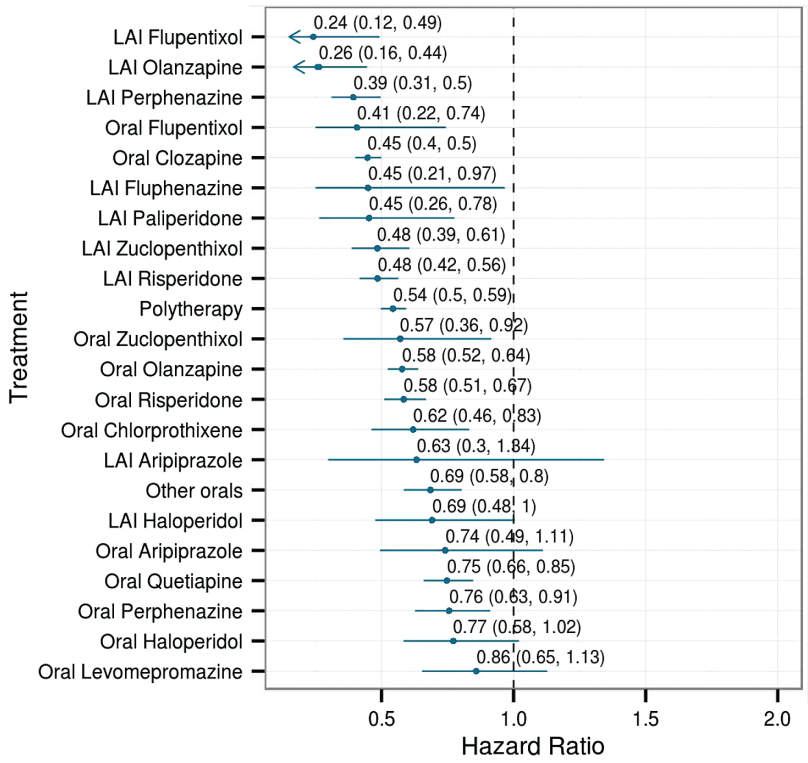

Fig. 2. Risk of psychiatric rehospitalization in monotherapy of specific antipsychotics in comparison to no use of antipsychotic in the incident cohort, within-individual model.

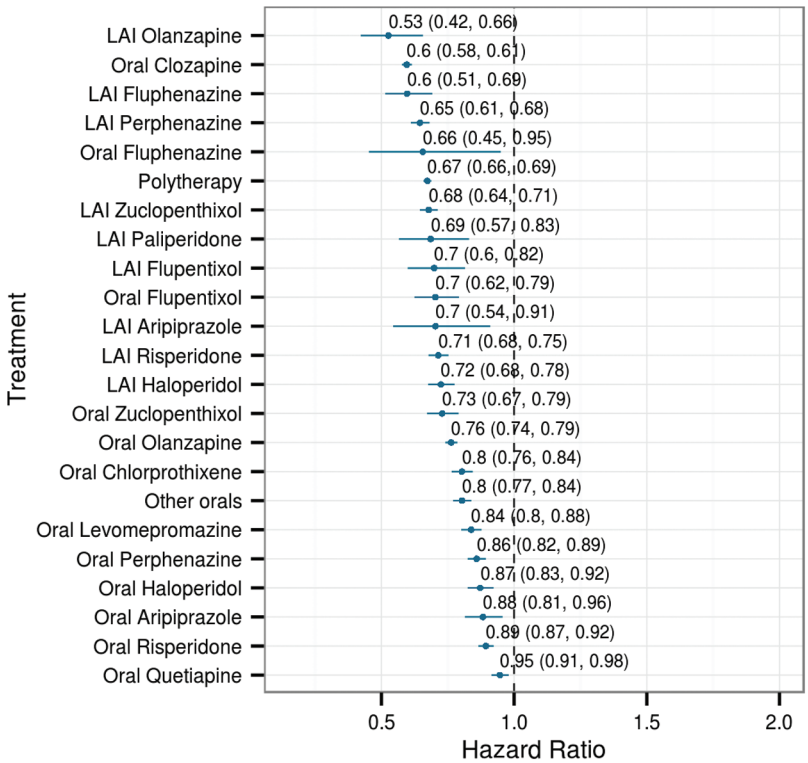

Fig. 3. Risk of all-cause hospitalization in monotherapy of specific antipsychotics in comparison to no use of antipsychotic in the prevalent cohort, within-individual model.

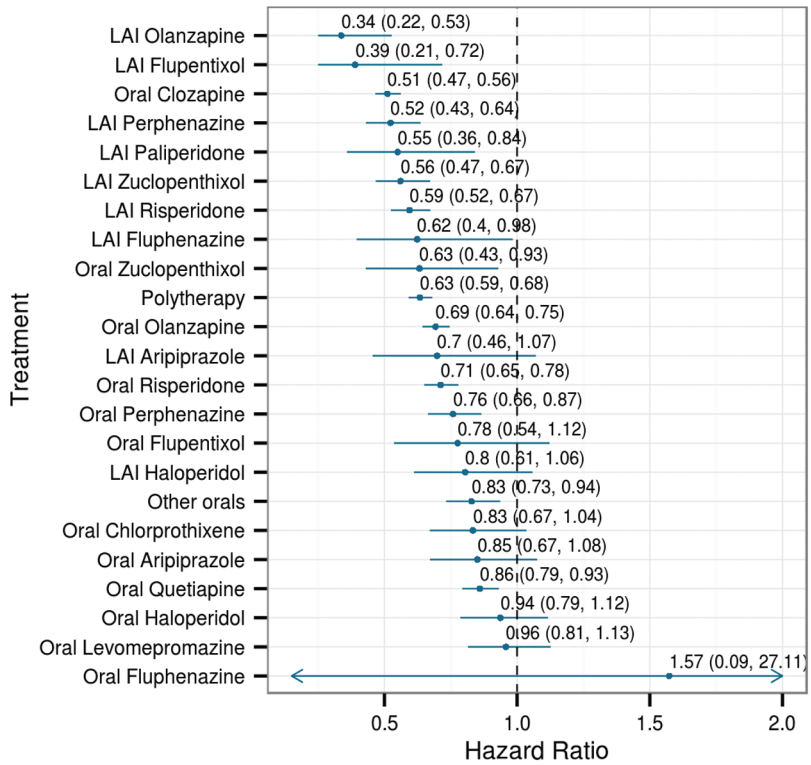

Fig. 4. Risk of all-cause hospitalization in monotherapy of specific antipsychotics in comparison to no use of antipsychotic in the incident cohort.

hospitalization risk when the same individual was using a specific antipsychotic to periods when no antipsychotic was used.

The same antipsychotics were associated with the lowest risks of both psychiatric and all-cause hospitalization. Thus, it seems that serious adverse effects associated with clozapine use, such as agranulocytosis and cardiovascular and metabolic effects,[14] are not leading to substantial excess of hospitalizations. Effectiveness of clozapine has been demonstrated in many previous studies[4,7–9] and meta-analysis of RCTs.[2] Previous studies have also shown that clozapine is associated with reduced mortality from both natural and unnatural causes despite these adverse effects.[15] Future studies are needed to better predict who will benefit from clozapine treatment in early stages of disease.

As in our previous study with within-individual analyses of antipsychotics,[9] the current study demonstrates that LAI use is associated with lower risk of psychiatric and all-cause hospitalizations. However, we also conducted head-to-head comparisons between LAI and corresponding oral formulation of the same drug and found that not all LAIs were substantially superior to orals in terms of psychiatric rehospitalization risk. Only risperidone, perphenazine, olanzapine, and haloperidol LAIs were associated with significantly lower risk than equivalent orals. Similar pattern was seen when antipsychotics were compared with oral olanzapine use, and not all LAIs were associated with lower risk of psychiatric rehospitalization than oral olanzapine except olanzapine and perphenazine LAIs. Thus, these results imply that there may be differences in effectiveness between LAIs, and the effectiveness of LAIs might not be explained purely by better adherence and closer health care controls (regular visits due to injections) which are related to all LAIs. This phenomenon may also be due to varying adherence to different oral antipsychotics or due to their pharmacological mechanisms as the references in these comparisons were the oral ones. In addition, half-lives of antipsychotics vary from each other which may impact the relative effectiveness of LAI vs the corresponding oral. The superiority of LAIs over orals in reducing the risk of psychiatric and all-cause hospitalization was almost identical for FGAs vs SGAs (HRs 0.46 vs 0.45 for psychiatric hospitalization, and 0.69 vs 0.70 for all-cause hospitalization).

Strengths of this study include within-individual analysis in which antipsychotics are compared within the same individual, excluding common sources of bias in observational studies such as selection bias. The results from secondary between-individual analysis were slightly different from the primary within-individual analysis, obviously because of residual confounding due to selection bias. Selection bias is related to multiple factors associated with treatment choice and many factors which cannot be found in register-based data (such as life style including

nutrition and smoking), severity of illness, or comorbid conditions and severity of symptoms, such as suicidality. In within-analysis, the impact of time invariant factors is removed, and duration of disease, the temporal order of treatments, and concomitant drug use are controlled for. Further strengths are related to unselected patient population, including all persons treated for schizophrenia within a country and without loss of follow-up, which are problems in RCTs. Our patient population is representative of real-life schizophrenia patients in outpatient care, while exclusion percentages in RCTs are often high and follow-up times short. As duration and timing of exposure is crucial in observational studies, a strength of our study was that drug use was modeled with PRE2DUP method which produces reliable estimates of drug use duration.[13,16] Our study limitations are related to registers which lack data on clinically important outcomes. Important issues such as quality of life should be assessed as our outcome measures were only related to hospitalizations as markers of overall effectiveness of pharmacotherapy.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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