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Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29 823 Patients With Schizophrenia

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IMPORTANCE It has remained unclear whether there are clinically meaningful differences between antipsychotic treatments with regard to preventing relapse of schizophrenia, owing to the impossibility of including large unselected patient populations in randomized clinical trials, as well as residual confounding from selection biases in observational studies.

OBJECTIVE To study the comparative real-world effectiveness of antipsychotic treatments for patients with schizophrenia.

DESIGN, SETTING, AND PARTICIPANTS Prospectively gathered nationwide databases were linked to study the risk of rehospitalization and treatment failure from July 1, 2006, to December 31, 2013, among all patients in Sweden with a schizophrenia diagnosis who were 16 to 64 years of age in 2006 (29 823 patients in the total prevalent cohort; 4603 in the incident cohort of newly diagnosed patients). Within-individual analyses were used for primary analyses, in which each individual was used as his or her own control to eliminate selection bias. Traditional Cox proportional hazards multivariate regression was used for secondary analyses.

MAIN OUTCOMES AND MEASURES Risk of rehospitalization and treatment failure (defined as psychiatric rehospitalization, suicide attempt, discontinuation or switch to other medication, or death).

RESULTS There were 29 823 patients (12 822 women and 17 001 men; mean [SD] age, 44.9 [12.0] years). During follow-up, 13 042 of 29 823 patients (43.7%) were rehospitalized, and 20 225 of 28 189 patients (71.7%) experienced treatment failure. The risk of psychiatric rehospitalization was the lowest during monotherapy with once-monthly long-acting injectable paliperidone (hazard ratio [HR], 0.51; 95% CI, 0.41-0.64), long-acting injectable zuclopenthixol (HR, 0.53; 95% CI, 0.48-0.57), clozapine (HR, 0.53; 95% CI, 0.48-0.58), long-acting injectable perphenazine (HR, 0.58; 95% CI, 0.52-0.65), and long-acting injectable olanzapine (HR, 0.58; 95% CI, 0.44-0.77) compared with no use of antipsychotic medication. Oral flupentixol (HR, 0.92; 95% CI, 0.74-1.14), quetiapine (HR, 0.91; 95% CI, 0.83-1.00), and oral perphenazine (HR, 0.86; 95% CI, 0.77-0.97) were associated with the highest risk of rehospitalization. Long-acting injectable antipsychotic medications were associated with substantially lower risk of rehospitalization compared with equivalent oral formulations (HR, 0.78; 95% CI, 0.72-0.84 in the total cohort; HR, 0.68; 95% CI, 0.53-0.86 in the incident cohort). Clozapine (HR, 0.58; 95% CI, 0.53-0.63) and all long-acting injectable antipsychotic medications (HRs 0.65-0.80) were associated with the lowest rates of treatment failure compared with the most widely used medication, oral olanzapine. The results of several sensitivity analyses were consistent with those of the primary analyses.

CONCLUSIONS AND RELEVANCE Clozapine and long-acting injectable antipsychotic medications were the pharmacologic treatments with the highest rates of prevention of relapse in schizophrenia. The risk of rehospitalization is about 20% to 30% lower during long-acting injectable treatments compared with equivalent oral formulations.

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Supplemental content

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The comparative effectiveness of antipsychotic treatments for patients with schizophrenia has remained controversial despite extensive research. Results from randomized clinical trials (RCTs) suggest that clozapine, olanzapine, and amisulpiride are superior to other antipsychotic medications in terms of efficacy.[1-3] However, the most efficacious drugs such as clozapine and olanzapine frequently induce adverse effects, such as weight gain and dyslipidemia, which may result in severe deterioration of health after long-term treatment. Investigation of these adverse effects or associated outcomes such as hospitalization and death requires thousands of patients and several years of follow-up to achieve enough statistical power, which is not possible for RCTs.

Another major issue in RCTs is the selection of patients. Those included in RCTs represent an atypical minority of the patient population because up to 80% to 90% of patients are excluded because of refusal, substance abuse, suicidal or antisocial behavior, or mental or physical comorbidity.[4] Especially problematic is the comparison of oral antipsychotic medications vs long-acting injections of antipsychotic medications because patients with the poorest adherence (ie, those who would receive the greatest benefit from long-acting injectable antipsychotic medications) are excluded from RCTs because participation is fully voluntary. Because RCTs include only an atypical fraction of the most adherent patients, they do not provide information on the real-world effectiveness of the antipsychotic treatments.

Observational studies can overcome some of the aforementioned problems by using nationwide electronic databases of hospitalization, mortality, and filled prescriptions. Previous large nationwide and statewide cohort studies have shown that clozapine, olanzapine, and long-acting injections of other antipsychotic medications are associated with better outcomes, that quetiapine is associated with suboptimal outcomes, and that use of antipsychotic medications is associated with lower mortality compared with no use.[5-14] However, the main problem with these observational studies is selection bias. Although the most important covariates such as sex, age, duration of illness, number of previous hospitalizations, and history of suicidal behavior and physical illness could be adjusted in the statistical analysis, there always remains residual confounding associated with the personal characteristics of each patient. We aimed to overcome this problem by using within-individual analysis, in which each person is his or her own control. In this approach, the exposure periods of each individual are compared with the nonexposure periods of the same individual. Therefore, the only factors that need to be adjusted are those that change as a function of time, such as time since cohort entry, temporal order of exposure periods, and concomitant medications. The objective of our study was to determine the effectiveness of antipsychotic treatments for the prevention of psychiatric rehospitalization and treatment failure in schizophrenia by applying within-individual analysis to a nationwide cohort of patients with schizophrenia.

Key Points

Question Are there any clinically meaningful differences between specific antipsychotic medications or routes of administration regarding the risk of psychiatric rehospitalization or other treatment failure?

Findings This database study of a nationwide cohort of patients using within-individual analysis to eliminate selection bias found that clozapine and long-acting injections of antipsychotic medications are associated with the lowest risk of rehospitalization and treatment failure.

Meaning Clozapine and long-acting injections of antipsychotic medications were the pharmacologic treatments with the highest rates of prevention of relapse in schizophrenia.

Methods

We used nationwide register-based data to conduct a prospective population-based cohort study of patients with schizophrenia, as previously described.[15] This research project was approved by the Regional Ethics Board of Stockholm (decision 2007/762-31). No informed consent is required for register-based studies using anonymized data.

Study Population

The nationwide source population included all individuals residing in Sweden who were 16 to 64 years of age in 2006 and who received a diagnosis of schizophrenia diagnosis during the period from July 1, 2006, to December 31, 2013 (prevalent cohort). Moreover, an incident cohort was derived of persons who received a diagnosis of schizophrenia for the first time. The flowchart of the cohort is shown in **Figure 1**, and the detailed information on the study population is shown in the eAppendix in the Supplement.

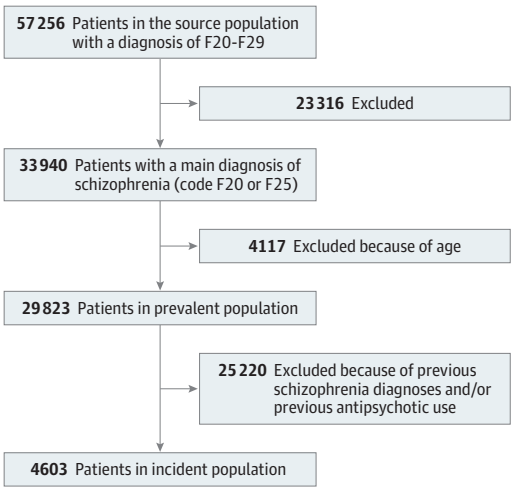
Exposure

Drug use from the Prescribed Drug Register included drugs prescribed during the period from 2005 to 2013 in outpatient care because drugs used in hospitals are not recorded in the registers. Drug use information in the register is categorized according to the Anatomical Therapeutic Chemical (ATC) classification,[16] and the purchased amount is recorded in defined daily dose (DDD) together with information on drug package and formulation. Antipsychotics were defined as ATC code N05A excluding lithium (ATC code N05AN01). Antipsychotics used by the study cohort were further divided according to drug formulation into oral antipsychotics and long-acting injectables. Antipsychotics were also categorized into first-generation and second-generation antipsychotics. The detailed description on the drug use modeling is shown in the eAppendix in the Supplement.

Outcomes

The main outcome measures in this study were psychiatric rehospitalization (including *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*

Figure 1. Flowchart of the Study Population



The diagnoses are indicated according to the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision, classification. F20 indicates schizophrenia; F21, schizotypal disorder; F22, persistent delusional disorders; F23, acute and transient psychotic disorders; F24, induced delusional disorder; F25, schizoaffective disorders; F28, other nonorganic psychotic disorders; and F29, unspecified nonorganic psychosis. A total of 23 316 patients were excluded because of having a diagnosis other than F20 or F25.

[*ICD-10*] codes F00-99) and treatment failure, defined as psychiatric rehospitalization (including admissions due to suicide attempts [*ICD-10* codes X60-84]), discontinuation or switch to other antipsychotic medication, or death. Because clozapine is typically the last treatment option, the probability of switching from clozapine to another antipsychotic medication may be low. Therefore, a secondary definition for treatment failure included only psychiatric rehospitalization, discontinuation of medication, or death (switch to another antipsychotic medication was excluded). Psychiatric hospitalization was derived from the National Patient Register as inpatient stay in the acute psychiatric ward or other psychiatric ward for at least 24 hours. Other outcomes were all-cause health care visits (inpatient stay or specialized outpatient visit).

Covariates

Within-individual models were adjusted for order of treatments, time since cohort entry, and antipsychotic medication polypharmacy. Comorbid conditions were identified from the National Patient Register, and drug use from the Prescribed Drug Register. The traditional Cox proportional hazards regression models were adjusted for sex, age at cohort entry, year of cohort entry, time since diagnosis, educational level, marital status, comorbidities, and drug use. The exact definitions are provided in the eTable 1 in the Supplement.

Statistical Analysis

All outcomes were recurrent and were analyzed with the within-individual Cox proportional hazards regression model as the main approach[17] (eFigure 1 in the Supplement). The within-individual model is a stratified Cox proportional hazards regression model in which each individual forms his or her own stratum. In addition, follow-up time is reset to zero after each outcome event to allow comparison of treatment periods within each individual. Within-individual analyses have been used in studies on psychotropic drug use and criminality.[17,18] We used the traditional multivariate-adjusted Cox proportional hazards regression model as secondary between-individual analyses. In within-individual analysis, only individuals with variation in the exposure and outcome contribute to the model, whereas in between-individual analysis, all individuals contribute to the model.

We compared the effectiveness of antipsychotics by considering (1) time receiving monotherapy only and (2) time receiving any therapy. In the first approach (considering time receiving monotherapy only), treatment periods were combined into a single variable indicating either monotherapy of a specified antipsychotic, polytherapy if any 2 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 happened during monotherapy with that antipsychotic and for polytherapy if 2 or more antipsychotics were used at the same time.

In the second approach (considering time receiving any therapy), treatment periods were defined by separate variables for each antipsychotic indicating either ongoing treatment or no use of that antipsychotic. In this analysis, events and risk time were accounted for a specific antipsychotic whenever that antipsychotic treatment was ongoing. In this approach, polytherapy was a separate variable that was adjusted for if 2 or more antipsychotics were used simultaneously. For treatment failure, oral olanzapine was used as a reference drug because it was the drug used most often in the study population. Treatment failure, indicated by discontinuation or switch of antipsychotic medication, cannot happen to nonusers; thus, nonuse was not included in this analysis. We conducted sensitivity analyses among the incident cohort to control for survival bias. When comparing the other antipsychotics (n = 20) with olanzapine, we set the level of significance at $P < .0025$.

Results

During the follow-up of the prevalent cohort, 13 042 of 29 823 patients (43.7%) experienced psychiatric rehospitalization and 20 225 of 28 189 patients (71.7%) had treatment failure. The mean duration of follow-up in the total cohort was 5.7 years (median, 6.9 years). The clinical and sociodemographic characteristics of the cohorts are described in eTable 2 in the Supplement. Oral olanzapine was the most frequently used drug, and zuclopenthixol the most frequently used as a long-acting injectable antipsychotic medication (eTable 3 in the Supplement).

The **Table** shows the incidence rates of psychiatric rehospitalization, and **Figure 2** shows the adjusted hazard ratios (HRs) during monotherapy. The HRs for the covariates used are shown in eTable 4 in the Supplement. The lowest risk of rehospitalization was observed for once-monthly long-acting injectable

Table. Incidence Rates of Psychiatric Rehospitalization During Monotherapy With Specific Antipsychotics

Characteristic	Prevalent Population			Incident Population		
	Person-years	Events, No.	Incidence Rate/10 Person-years (95% CI)	Person-years	Events, No.	Incidence Rate/10 Person-years (95% CI)
No use	30 209	9675	3.2 (3.1-3.3)	6723	1456	2.2 (2.1-2.3)
First-generation LAI medications						
Fluphenazine	329	56	1.7 (1.3-2.2)	3	0	NA
Flupentixol	1589	430	2.7 (2.5-3.0)	46	11	2.4 (1.3-4.3)
Haloperidol	2655	726	2.7 (2.5-2.9)	77	25	3.2 (2.2-4.8)
Perphenazine	4937	1318	2.7 (2.5-2.8)	272	59	2.2 (1.7-2.8)
Zuclopenthixol	6149	1709	2.8 (2.7-2.9)	162	58	3.6 (2.8-4.6)
First-generation oral formulations						
Flupentixol	2415	291	1.2 (1.1-1.4)	89	25	2.8 (1.9-4.2)
Haloperidol	3334	674	2.0 (1.9-2.2)	186	65	3.5 (2.7-4.5)
Levomepromazine	1120	410	3.7 (3.3-4.0)	90	33	3.7 (2.6-5.1)
Perphenazine	3374	848	2.5 (2.4-2.7)	186	51	2.7 (2.1-3.6)
Zuclopenthixol	3381	686	2.0 (1.9-2.2)	101	32	3.2 (2.2-4.5)
Second-generation LAI medications						
Olanzapine	244	137	5.6 (4.8-6.7)	58	18	3.1 (2.0-4.9)
Paliperidone[a]	480	155	3.2 (2.8-3.8)	120	36	3.0 (2.2-4.2)
Risperidone	4359	1245	2.9 (2.7-3.0)	330	83	2.5 (2.1-3.2)
Second-generation oral formulations						
Aripiprazole	5661	1276	2.3 (2.1-2.4)	855	153	1.8 (1.5-2.1)
Clozapine	14 198	2635	1.9 (1.8-1.9)	368	92	2.5 (2.0-3.1)
Olanzapine	19 486	3312	1.7 (1.6-1.8)	1665	335	2.0 (1.8-2.2)
Quetiapine	4343	1643	3.8 (3.6-4.0)	806	194	2.4 (2.1-2.8)
Risperidone	11 184	1638	1.5 (1.4-1.5)	848	187	2.2 (1.9-2.6)
Other	2889	693	2.4 (2.2-2.6)	288	83	2.9 (2.3-3.6)
Polytherapy	43 605	17 193	3.9 (3.9-4.0)	2107	930	4.4 (4.1-4.7)

Abbreviations: LAI, long-acting injectable; NA, not applicable.

[a] Paliperidone is a once-monthly injection.

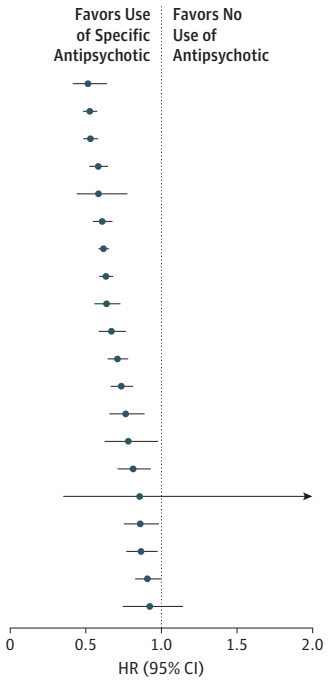
paliperidone (HR, 0.51; 95% CI, 0.41-0.64), long-acting injectable zuclopenthixol (HR, 0.53; 95% CI, 0.48-0.57), clozapine (HR, 0.53; 95% CI, 0.48-0.58), long-acting injectable perphenazine (HR, 0.58; 95% CI, 0.52-0.65), and long-acting injectable olanzapine (HR, 0.58; 95% CI, 0.44-0.77) (Figure 2). The highest risk of rehospitalization was seen with oral flupentixol (HR, 0.92; 95% CI, 0.74-1.14) and quetiapine (HR, 0.91; 95% CI, 0.83-1.00). When adjusting for the use of concomitant antidepressant and benzodiazepine use, we found that the results remained almost identical (eFigure 2 in the Supplement). When compared with the most frequently used antipsychotic, oral olanzapine, clozapine (HR, 0.84; 95% CI, 0.76-0.93; $P < .001$), and long-acting injectable zuclopenthixol (0.83; 0.75-0.92; $P < .001$) were associated with significantly lower risk of rehospitalization, and oral flupentixol (HR, 1.46; 95% CI, 1.17-1.82; $P < .001$), quetiapine (HR, 1.43; 95% CI, 1.29-1.59; $P < .001$), and oral haloperidol (HR, 1.28; 95% CI, 1.12-1.48; $P < .001$) were associated with a significantly higher risk of rehospitalization after Bonferroni correction. In within-individual analysis, the risk of rehospitalization was 22% lower during use of long-acting injectable antipsychotic medications compared with use of corresponding oral formulations (HR, 0.78; 95% CI, 0.72-0.84; $P < .001$).

The incidence rates of treatment failure during each monotherapy compared with oral olanzapine are shown in eTable 5 in the Supplement, and the adjusted HRs of treatment failure during each monotherapy compared with oral olanzapine are shown in **Figure 3**. The lowest risk of treatment failure was observed for clozapine (HR, 0.58; 95% CI, 0.53-0.63), and the second lowest was seen for all long-acting injectable antipsychotic medications (HRs, 0.65-0.80), whereas the highest risk was seen for levomepromazine (HR, 1.15; 95% CI, 1.02-1.28). When adjusting for the concomitant use of antidepressants and benzodiazepines, we found that the results remained the same (eFigure 3 in the Supplement). A secondary head-to-head analysis including only patients who had used oral olanzapine during the follow-up showed almost identical rank order (eFigure 4 in the Supplement). When a switch to another antipsychotic medication was not included in the definition of treatment failure, clozapine was still associated with the best outcome (HR, 0.58; 95% CI, 0.53-0.64) compared with oral olanzapine.

The corresponding results for psychiatric rehospitalization and treatment failure during any specific treatment (also other treatment periods than monotherapy included in the analysis) are shown in eTables 6 and 7 and eFigures 5 and 6 in

Figure 2. Adjusted Hazard Ratios (HRs) and 95% CIs for Psychiatric Rehospitalization During Monotherapy Compared With No Use of Antipsychotic in Within-Individual Analyses in the Prevalent Population

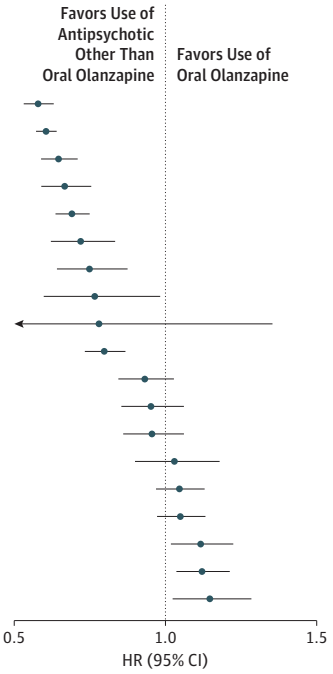
Treatment	HR (95% CI)
LAI paliperidone	0.51 (0.41-0.64)
LAI zuclopenthixol	0.53 (0.48-0.57)
Oral clozapine	0.53 (0.48-0.58)
LAI perphenazine	0.58 (0.52-0.65)
LAI olanzapine	0.58 (0.44-0.77)
LAI risperidone	0.61 (0.55-0.68)
Polytherapy	0.62 (0.58-0.65)
Oral olanzapine	0.63 (0.59-0.68)
LAI haloperidol	0.64 (0.56-0.73)
Oral zuclopenthixol	0.67 (0.59-0.76)
Oral risperidone	0.71 (0.64-0.78)
Oral aripiprazole	0.73 (0.66-0.81)
Oral levomepromazine	0.76 (0.66-0.89)
LAI flupentixol	0.78 (0.62-0.98)
Oral haloperidol	0.81 (0.71-0.93)
LAI fluphenazine	0.86 (0.35-2.08)
Other oral formulations	0.86 (0.75-0.98)
Oral perphenazine	0.86 (0.77-0.97)
Oral quetiapine	0.91 (0.83-1.00)
Oral flupentixol	0.92 (0.74-1.14)



Paliperidone long-acting injectable (LAI) is a once-monthly injection. The vertical dashed line shows the reference value (no use of antipsychotic). The arrow indicates that the higher end of the 95% CI (2.08) is beyond the scale (up to 2.00).

Figure 3. Adjusted Hazard Ratios (HRs) and 95% CIs for Treatment Failure During Each Monotherapy Compared With Oral Olanzapine Use

Treatment	HR (95% CI)
Oral clozapine	0.58 (0.53-0.63)
Polytherapy	0.61 (0.57-0.64)
LAI perphenazine	0.65 (0.59-0.71)
LAI haloperidol	0.67 (0.59-0.75)
LAI zuclopenthixol	0.69 (0.64-0.75)
LAI paliperidone	0.72 (0.62-0.83)
LAI flupentixol	0.75 (0.64-0.87)
LAI olanzapine	0.77 (0.60-0.98)
LAI fluphenazine	0.78 (0.45-1.35)
LAI risperidone	0.80 (0.73-0.87)
Oral perphenazine	0.93 (0.84-1.03)
Oral zuclopenthixol	0.95 (0.85-1.06)
Oral haloperidol	0.96 (0.86-1.06)
Oral flupentixol	1.03 (0.90-1.18)
Oral quetiapine	1.05 (0.97-1.13)
Oral risperidone	1.05 (0.97-1.13)
Other oral formulations	1.12 (1.02-1.22)
Oral aripiprazole	1.12 (1.04-1.21)
Oral levomepromazine	1.15 (1.02-1.28)



Clozapine ($P < .001$), long-acting injectable (LAI) perphenazine ($P < .001$), LAI haloperidol ($P < .001$), LAI zuclopenthixol ($P < .001$), LAI paliperidone ($P < .001$), LAI flupentixol ($P < .001$), and LAI risperidone ($P < .001$) differed significantly from oral olanzapine after Bonferroni correction. The vertical dashed line shows the reference value (oral olanzapine use). The arrow indicates that the lower end of the 95% CI (0.45) is beyond the scale (to 0.50).

the Supplement. Similar results as those for monotherapy were found and are presented in the correlation plot for these analyses regarding psychiatric rehospitalization in eFigure 7 in the Supplement. Data on the most common combinations of antipsychotic polypharmacy are shown in eTable 8 in the Supplement. The analysis on all-cause inpatient or outpatient visits revealed the lowest risk for clozapine (HR, 0.87; 95% CI, 0.83-0.91) (eFigure 8 in the Supplement).

The results observed in secondary between-individual analysis for psychiatric rehospitalization and treatment failure are shown in eFigures 9 and 10 in the Supplement. The results of sensitivity analysis regarding psychiatric rehospitalization and treatment failure among the incident cohort are shown in the Table and eTable 5 in the Supplement, and adjusted risks are shown in eFigures 11 and 12 in the Supplement. In the incident cohort, the risk of psychiatric rehospitalization was 32% lower during treatment with long-acting injectable antipsychotic medications compared with treatment with equivalent oral formulations (HR, 0.68; 95% CI, 0.53-0.86).

Discussion

To our knowledge, this is the first study to investigate the comparative effectiveness of antipsychotic treatments for patients with schizophrenia using within-individual Cox proportional hazards regression analysis. This method enables correction for selection biases because each individual serves as his or her own control. For example, if individuals willing to use clozapine or long-acting injectable antipsychotic medications differed from other patients concerning the intrinsic severity of their illness or adherence with treatment, the putative bias is eliminated by comparing the risk during use of a specific medication with the risk during no use of that medication within the same individual. The association of time-dependent factors such as duration of the disease, use of concomitant medications, and temporal order of exposure and nonexposure periods (such as a switch from an oral formulation to a long-acting injectable antipsychotic medication vs from a long-acting injectable antipsychotic medication to an oral formulation) with relapse of schizophrenia was taken into account. Although continuous use of antipsychotics is recommended for the prevention of relapse of schizophrenia, treatments are often started when the patient's clinical state deteriorates, and, therefore, the HRs may be slightly overestimated for all treatments. However, it is unlikely that there would be systematic differences between different medications in this regard.

Our results from a large nationwide cohort show that clozapine and long-acting injectable antipsychotic medications are substantially more effective than other antipsychotics in reducing the risk of rehospitalization or any treatment failure. The most consistent findings were observed for clozapine, being the first in rank order in most of the analyses. These results are in line with those of previous cohort studies using traditional between-individual analyses,[6,8,14,19] although the effect sizes differed to some extent, especially for comparisons between long-acting injectable antipsychotic medications and corresponding oral formulations. Our results showed that the risk of rehospitalization was 22% lower during treatment with long-acting injectable antipsychotic medications compared with treatment with equivalent oral formulations in the total cohort and 32% lower in the incident cohort of newly diagnosed patients. This finding is in line with those of Alphs et al,[20] indicating that use of long-acting injectable antipsychotic medications results in the greatest benefit during the early phase of the illness. Previous RCTs comparing long-acting injectable antipsychotic medications and oral formulations among patients with chronic schizophrenia have not found significant differences,[21,22] probably owing to the fact that patients having the biggest potential benefit are not included in RCTs.

However, the first direct comparison of long-acting injectable antipsychotic medication vs oral formulation of the same second-generation antipsychotic for patients with their first episode of schizophrenia found that the use of long-acting injectable antipsychotic medication was associated with an 85% lower risk of relapse,[23] which also suggests that the greatest benefit of long-acting injectable antipsychotic medications is achieved among newly diagnosed patients. The sensitivity analyses among our incident cohort, as well as the use of traditional between-individual analyses, gave rather similar results as those of the primary within-individual analyses among the total cohort. Head-to-head analyses restricted to patients who used olanzapine, as well as analyses using monotherapy and any therapy including polypharmacy, also showed consistent outcomes. The results were similar for rehospitalization and treatment failure (also including discontinuation or switch of medication), which suggests that the good outcomes are mediated by good adherence. The better outcomes associated with clozapine and long-acting injectable antipsychotic medications may be partly explained by the more regular contact with medical staff necessitated by blood samples and injections. However, from the view of patients and their families, it is irrelevant which specific factor in the chosen treatment plan contributes most to the outcome. From a societal perspective, more frequent visits to a health care professional increase costs, but as the savings from decreased rehospitalization are much greater, the economical net effect is positive.

It is remarkable that the risk of psychiatric rehospitalization, being a marker for relapse, was about 40% to 70% higher during monotherapy with quetiapine than during monotherapy with clozapine, oral olanzapine, or the most frequently used long-acting injectable antipsychotic medications. Because 44% of patients were rehospitalized, the differences in the observed HRs correspond to substantial differences in absolute risks. Quetiapine has been the most commonly used antipsychotic in many countries. Although dosing was probably too low when it was initially introduced, that was not the case during the follow-up of our study (average dose, 360 mg/d, equaling 0.90 DDD/d). Our results are in line with those of previous studies[8,14] suggesting that quetiapine should not be used routinely as monotherapy for patients with schizophrenia without specific reasons. Although between-individual analysis gave otherwise consistent results compared with within-individual analyses, the results for oral flupentixol were substantially more favorable in the between-individual analysis for risk of psychiatric rehospitalization.

This finding suggests that this agent was used among patients with a lower intrinsic risk of relapse (which was the case as can be seen in the Table) and that between-individual analysis was not able to fully adjust for this factor. This finding is in line with the fact that oral flupentixol was used in low doses

(mean dose, 2.1 mg/d, equaling 0.35 DDD/d), which may explain its relatively low effectiveness in the primary within-individual analysis. Although long-acting injectable zuclopenthixol was among the drugs associated with the lowest risk of psychiatric rehospitalization, this finding does not take into account the frequency of extrapyramidal adverse effects that may affect patients' quality of life. The effect of each individual's adherence to treatment was adjusted in the between-individual analysis. Also, in this analysis, long-acting injectable antipsychotic medications except olanzapine and flupenthixol (relatively few patients and large CIs) were associated with a lower risk of psychiatric rehospitalization or treatment failure. However, it is probable that adherence is a major factor explaining better outcomes with long-acting injectable antipsychotic medications, and the rationale for developing long-acting injectable formulations was to improve adherence. Our results show that many first-generation oral formulations of antipsychotic medications were used at low doses. Because our data are not about the prescribed doses but about the actual mean amount of purchased medications during the follow-up, it is plausible that patients may have adjusted their oral doses lower than prescribed, while this is not possible when long-acting injectable antipsychotic medications are used.

Strengths and Limitations

The strength of observational studies using nationwide databases is that there are no missing data on rehospitalization or treatment failure, whereas in RCTs, the dropout rates are about 50% to 60% of the patients, leading to missing data.[24] Our database did not include information on symptoms, functioning, tardive dyskinesia, or quality of life; therefore, rehospitalization and treatment failure were the only outcome measures. Although time-dependent factors such as aging are adjusted in the within-individual analysis, there always remains the possibility of residual confounding associated with the passing of calendar time. For example, we did not have data on concomitant treatment with psychological therapies or on the use of mood stabilizers. However, it is unlikely that there would be systematic differences between antipsychotics in this regard. The strengths of this study include nationwide coverage of patients with schizophrenia in a real-life setting and complete coverage of drug purchases from register-based data.

Within-individual analyses fully adjust for patient-related characteristics that may affect drug effectiveness and tolerability. Observational mirror-image studies also do this, but their major limitation is that patients switch from oral formulations to long-acting injectable antipsychotic medications (not vice versa), and the effect of temporal order cannot be controlled. As only those experiencing an adverse event and having variation in the exposure are included in the within-individual analyses, we also conducted between-individual comparisons including all patients, which revealed similar results as the primary analyses. Survival bias was eliminated by restricting secondary analyses to incident cases. Drug use was modeled with the state-of-the-art Prescriptions to Drug Use Periods (PRE2DUP) method, which describes actual drug use well when compared with interview-reported use.[25] Our results on the comparative effectiveness of specific antipsychotics can be generalized only to white populations and high-income countries in which all antipsychotic treatments are reimbursed by the state.

Conclusions

Our results suggest that there are substantial differences between specific antipsychotic agents and between routes of administration concerning the risk of rehospitalization and treatment failure among patients with schizophrenia.

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