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The Cumulative Effect of Antipsychotic Usage on Mortality in Schizophrenia: A Nationwide Population-based Cohort Study in Korea

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Objective: To investigate the cumulative effect of antipsychotics at different dosages on mortality in patients with schizophrenia.
Methods: We analyzed data from the Korean National Health Insurance System−National Sample Cohort covering the 2002−2013 period. We used Cox regression analysis to calculate hazard ratios for mortality risks according to cumulative antipsychotic exposure levels (low, moderate, and high).
Results: Our analyses revealed no significant association between antipsychotic exposure and mortality (either all-cause or cause-specific) in patients with schizophrenia.
Conclusion: Our results imply that the excess mortality of patients with schizophrenia is attributable to factors other than antipsychotic usage.

KEY WORDS: Schizophrenia; Antipsychotics; Mortality; South Korea.

INTRODUCTION

Schizophrenia is a mental disorder that features symptoms such as delusions, hallucinations, and disorganized speech and behavior, and it causes multifaceted dysfunction in life [1]. The median lifetime prevalence rate of schizophrenia is reported as 0.48% (interquartile range, 0.34−0.85%) [2]. In spite of the low prevalence rate, the burden that schizophrenia places on patients, family members, and society is tremendous [3]. According to the Global Burden of Disease Study 2017, there were 1.13 million incident cases of schizophrenia and 12.66 million (95% uncertainty interval, 9.48−15.56 million) disability-adjusted life years due to schizophrenia in 2017 [4].

One of the major burdens of schizophrenia is premature mortality [5]. Patients with schizophrenia have a higher risk of all-cause mortality and mortality due to specific causes (e.g., cardiovascular disease, neoplasm, and suicide) when compared with the general population [6,7]. This premature mortality has generally been attributed to factors such as unhealthy lifestyles, alcohol and substance abuse, and comorbid somatic diseases [6,8]. Another factor potentially related to mortality in patients with schizophrenia is their antipsychotic usage, but the literature contains mixed results. A systematic review suggested that long-term usage of antipsychotics may increase mortality [9], but other studies have found that exposure (any, current, or cumulative) to antipsychotics reduces mortality risks [10-15]. Moreover, a recent study from Sweden [16] found that exposure to antipsychotics exhibited a U-shaped association with all-cause mortality, with the no-usage group having the highest overall mortality rate followed by the high-exposure group. The authors suggested that adequate antipsychotic dosages (low or moderate) lower mortality risks for patients with schizophrenia and that excess mortality of patients with schizophrenia is due to other factors, not antipsychotic usage [16].

However, studies on the effect of antipsychotics on

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mortality in patients with schizophrenia are scarce, and studies on the cumulative dose-specific effects of antipsychotics on mortality are rare. It is thus difficult to draw firm conclusions on the cumulative dose-specific effects of antipsychotics on mortality. We therefore conducted a nationwide population-based cohort study to investigate the cumulative dose-specific effects of antipsychotics on all-cause and cause-specific mortality in patients with schizophrenia in the Republic of Korea.

METHODS

We conducted this study with data from the Korean National Health Insurance System-National Sample Cohort (NHIS-NSC) provided by the Korean National Health Insurance Corporation. The Korean NHIS system, which was established for claims reimbursement purposes, includes the entire national population (approximately 50 million people). For representative sampling of the NHIS data, 756 strata based on 18 groups for age, 21 groups for income level by insurance type, and two groups for sex were set up with data from 2002. The NHIS-NSC data sample includes 1,025,340 individuals, which is equivalent to 2.2% of all NHIS members in 2002.

For the present study, we selected individuals from the NHIS-NSC dataset who had at least one primary diagnosis (outpatient or inpatient) for the International Classification of Diseases, 10th Revision (ICD-10) codes of F20 to F25, which correspond to schizophrenia and related diagnoses. In total, 9,978 individuals were included in the present study. We followed these individuals from their initial diagnosis dates until death or December 31, 2013, whichever came first. Whether the patients were still alive on December 31, 2013, was determined by linkage to the database of the Statistics Korea and the specific cause of mortality was recorded based on the ICD-10 codes. The outcomes of interest were all-cause mortality (ICD-10 codes A00 to Z99) and three specific causes of mortality: suicide (ICD-10 codes X60 to X84), cardiovascular disease (ICD-10 codes I00 to I99), and neoplasms (ICD-10 codes C00 to D49).

Antipsychotic usage levels were determined based on prescription records from the observation period. Prescription drugs were classified according to the Anatomical Therapeutic Chemical coding system, under which antipsychotics are coded as N05A; antidepressants are coded as N06AA, N06AB, N06AG, or N06AX; and benzodiazepines are coded as N03AE, N05BA, or N05CD. The antipsychotic drugs investigated in this study included amisulpride, aripiprazole, chlorpromazine, clozapine, haloperidol, levomepromazine, olanzapine, paliperidone, perphenazine, pimozide, quetiapine, risperidone, sulpiride, ziprasidone, and zotepine. The prescribed medication doses were estimated based on defined daily doses (DDDs), and cumulative antipsychotic doses were calculated by multiplying the prescribed medication dose by the number of prescription days and dividing by the DDD. If a participant was prescribed with more than one antipsychotic medication, all antipsychotic medication that the participants were prescribed with was considered when calculating the cumulative DDD. For instance, if a participant has been prescribed with 100 mg of Olanzapine ($DDD_{Olanzapine}$ = 10 mg, cumulative $DDD_{olanzapine}$ = 100 mg/10 mg = 10DDD) and 6,000 mg of Clozapine ($DDD_{clozapine}$ = 300 mg, cumulative $DDD_{clozapine}$ = 6,000 mg/300 mg = 20DDD) during the follow up period, this participants' cumulative DDD (cDDD) would be 30 DDD. The selected individuals were categorized into four cDDD groups: 1) non-use, defined as no antipsychotic usage during the observation period; 2) low-dose, defined as having a nonzero daily cDDD under 0.5; 3) moderate-dose, defined as having a daily cDDD of 0.5 to 1.5; and 4) high-dose, defined as having a daily cDDD greater than 1.5. This categorization scheme was used in a previous study [15].

The selected individuals were also categorized into 5-year age groups (age of diagnosis), and the Charlson Comorbidity Index (CCI) [17] was calculated for each individual. Under the CCI system, certain physical diseases (e.g., diabetes, tumor, etc.) have their own weight based on their severity. A score of 0 indicates that an individual does not have a comorbid disease, and higher CCI scores indicate that the patient has multiple comorbid diseases or a severe disease.

This study was approved by the Institutional Review Board of the National Center for Mental Health (116271-2021-09).

Statistical Analysis

To quantify the associations between antipsychotic cDDD groups and mortality rates, we used Cox regression analysis to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). The no-use condition consistently

served as the reference group in HR calculations. Our Cox regression analysis included adjustments for sex, age, use of other medications (antidepressants and benzodiazepines), and CCI scores [15]. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA), and p values less than or equal to 0.05 were considered statistically significant.

RESULTS

The descriptive characteristics of the included individuals are presented in Table 1. The adjusted hazard ratios for all-cause and cause-specific mortality according to different antipsychotic exposure levels are listed in Table 2.

Before controlling for sex, age, use of other medications, and CCI scores, high-dose antipsychotic usage was associated with a reduced risk of all-cause mortality (crude HR [CHR] = 0.56, 95% CI = 0.42−0.75) and mortality due to cardiovascular disease (CHR = 0.35, 95% CI = 0.16−0.74), and moderate-dose usage was associated with a lower

Table 1. Characteristics of the patient sample

Characteristics	Number (%)
Age (yr)	
0−19	432 (5.60)
20−29	1,313 (17.03)
30−39	1,711 (22.19)
40−49	1,806 (23.42)
50−59	1,080 (14.00)
60−69	699 (9.06)
≥ 70	671 (8.70)
Sex	
Male	3,807 (49.36)
Female	3,905 (50.64)
Charlson Comorbidity Index	
0	2,057 (26.67)
1	2,050 (26.58)
2	1,435 (18.61)
≥ 3	2,170 (28.14)
Antipsychotic exposure	
No use	657 (8.52)
Low use	2,316 (30.03)
Moderate use	3,201 (41.51)
High use	1,538 (19.94)
Cause of mortality	
All-cause	842 (10.92)
Cause-specific	
Cardiovascular disease	162 (19.24)
Suicide	166 (19.71)
Neoplasms	105 (12.47)

Table 2. Causes of mortality and association with cumulative antipsychotic doses

Cause of mortality	No use (n = 657)		Low dose (n = 2,316)			Moderate dose (n = 3,201)			High dose (n = 1,538)			Use (combined) (n = 7,055)		
	Deaths (n)	Deaths (n)	Crude HR (95% CI)	aHR (95% CI)	Deaths (n)	Crude HR (95% CI)	aHR (95% CI)	Deaths (n)	Crude HR (95% CI)	aHR (95% CI)	Deaths (n)	Crude HR (95% CI)	aHR (95% CI)
All-cause	76	345	1.23 (0.96−1.57)	1.05 (0.82−1.35)	306	0.71 (0.55−0.91)	1.14 (0.88−1.47)	115	0.56 (0.42−0.75)	1.22 (0.91−1.65)	766	0.84 (0.66−1.06)	1.11 (0.87−1.40)
Cardiovascular disease	14	88	1.72 (0.98−3.02)	1.34 (0.76−2.38)	47	0.60 (0.33−1.09)	1.23 (0.67−2.24)	13	0.35 (0.16−0.74)	1.26 (0.58−2.75)	148	0.89 (0.51−1.54)	1.30 (0.75−2.25)
Suicide	12	38	0.86 (0.45−1.65)	0.90 (0.46−1.73)	76	1.13 (0.61−2.07)	1.02 (0.55−1.91)	40	1.25 (0.66−2.39)	1.09 (0.56−2.11)	154	1.07 (0.60−1.93)	1.00 (0.55−1.82)
Neoplasms	6	48	2.12 (0.91−4.94)	1.54 (0.66−3.61)	40	1.13 (0.48−2.66)	1.93 (0.81−4.57)	11	0.66 (0.24−1.78)	2.07 (0.75−5.71)	99	1.32 (0.58−3.02)	1.72 (0.76−3.93)

The antipsychotic no-use group was used as a reference group for all HR calculations.
HR, hazard ratio; aHR, HR adjusted for sex, age group, use of medications (i.e., antidepressants, benzodiazepines), and CCI; CCI, Charlson Comorbidity Index; CI, confidence interval.

risk of all-cause mortality (CHR = 0.71, 95% CI = 0.55–0.91). However, these associations disappeared after controlling for the covariates.

DISCUSSION

In this population-based cohort study, we investigated the effect of cumulative antipsychotic usage on all-cause and cause-specific mortality in patients with schizophrenia. After controlling for covariates, there was no significant association between antipsychotic usage at any dosage level and all-cause or cause-specific mortality in patients with schizophrenia.

Previous studies suggest that the use of clozapine [18,19] or long-acting injection antipsychotic drugs [20,21] lowers the mortality of those with schizophrenia. However, to date, only a few studies have examined the effect of cumulative antipsychotic usage on mortality in patients with schizophrenia and more research needs to be done to achieve consensus on the cumulative effect of antipsychotic use in schizophrenia mortality. These studies generally reported that antipsychotic usage lowered mortality risks in patients with schizophrenia, although dose-specific effects varied between studies. Two studies from Sweden [15] and Finland [18] found that moderate and high doses of antipsychotics were associated with reduced overall mortality for patients with schizophrenia. Another study from Sweden [16] found that low and moderate antipsychotic doses were associated with reduced mortality risks for patients with schizophrenia. Taipale *et al.* [18] suggested that antipsychotic usage reduces mortality by alleviating the symptoms of schizophrenia. Moreover, antipsychotic usage lowers cardiovascular mortality by reducing unhealthy behaviors (e.g., smoking and alcohol abuse) and stress [22-24]. Our findings also imply that excess mortality in schizophrenia may be attributable to factors other than antipsychotic treatment, which is in line with a previous study's findings [16]. It is generally believed that excess mortality in patients with schizophrenia is largely attributable to unhealthy lifestyle factors, such as smoking, alcohol abuse, poor diet, and lack of exercise [25]. However, the factors associated with mortality in patients with schizophrenia remain unclear. Future studies are needed to identify these various factors.

This study had several limitations. First, we conducted a retrospective cohort study utilizing a national registry data. Therefore, there were limited information that was retrievable (e.g., the severity of schizophrenia could not be measured), and the presence or absence of each disease was classified based solely on ICD-10 codes. Second, because we only had access to data concerning physician-issued prescriptions, we could not determine the degree of adherence to antipsychotic therapy. Last but not least, the NHIS-NSC is comprised of 2% of the entire population in Korea and schizophrenia is a mental disorder with a relatively low prevalence rate. Therefore, future studies need to be conducted while utilizing the entire population in Korea to confirm the results found in this study. The main strength of our study is that it used a nationally representative sample.

In conclusion, our results indicate that there is no significant association between antipsychotic usage at any dosage level and all-cause or cause-specific mortality in patients with schizophrenia. This implies that the excess mortality of patients with schizophrenia is attributable to factors other than antipsychotic use.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Subin Park, Gyurin Kim. Methodology: Minkyung Jo. Statistical analysis: Min Geu Lee. Reference review: Gyurin Kim, Soo Jung Rim, Se Jin Park. Writing–original draft: Gyurin Kim, Soo Jung Rim, Se Jin Park, Min Geu Lee. Writing–review and editing: Subin Park, Se Jin Park, Soo Jung Rim. Approval of final manuscript: all authors.

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