Antipsychotic Prescribing Patterns in First-episode Schizophrenia: A Five-year Comparison

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Objective: Early treatment choice is critical in first-episode schizophrenia-spectrum disorders. The purpose of this study was to describe prescribing trends of antipsychotics use in patients with first-episode schizophrenia in 2005 and 2010, respectively.
Methods: We reviewed the medical records of newly treated patients with schizophrenia from a university psychiatric hospital in 2005 (n=47) and 2010 (n=52). We defined patients as receiving a high antipsychotic dose if their ratio of prescribed daily dose (PDD) to defined daily dose (DDD) was greater than 1.5.
Results: The rates of high-dose antipsychotic prescription were 61.7% and 53.8% in 2005 and 2010, respectively. The rates of antipsychotic polypharmacy were 34.6% in 2005 and 34.0% in 2010. The most common first-prescribed antipsychotics were (in descending order of prescription frequency) olanzapine, risperidone, aripiprazole, and haloperidol in 2005 and risperidone, quetiapine, paliperidone, and olanzapine in 2010. High-dose antipsychotics were significantly associated with antipsychotic polypharmacy (odds ratio=23.97; $p<0.01$). More individuals were treated with mood stabilizers in 2010 than in 2005 ($p=0.003$).
Conclusion: The practice of prescribing high-dose antipsychotics and associated antipsychotic polypharmacy were common even for initial treatment of first-episode schizophrenia in 2005 and 2010. In 2010, the list of the most common first-prescribed antipsychotics changed, and the use of mood stabilizers increased in non-affective schizophrenia.

KEY WORDS: Schizophrenia; Antipsychotic agents; Polypharmacy; First-episode; Antimanic agents.

INTRODUCTION

The onset of schizophrenia illness typically occurs in late adolescence or early adulthood, with patients showing neurodevelopmental alterations as well as a progressive decline in overall functions.[1] The deterioration is evident in psychopathological, neurocognitive, and functional areas following the initial onset of a psychotic episode. Lifetime maintenance therapy may improve social functioning and prevent symptom relapse; however, the therapy also causes significant public health problems and economic costs.[2] Pharmacological intervention is most efficacious during the first 5 years of illness,[3] and the chance of responding to treatment decreases over time.[4]

The initial response to medication within the first 1-3 months is highly predictive of long-term disease consequences.[5] In this context, the choice of antipsychotic drug is important for first-episode psychosis treatment.

Despite numerous trials investigating first-episode psychosis treatment, no specific drug has been proven to be superior in terms of overall efficacy, with the exception of clozapine in patients with neuroleptic-refractory schizophrenia.[6] Currently, schizophrenia treatment guidelines recommend second-generation antipsychotics (SGAs) as first-line medications,[7-9] as they are associated with fewer extrapyramidal symptoms (EPS) and other favorable side effect profiles. The trend toward more frequent use of SGAs over first-generation antipsychotics (FGAs) from the 1990s to the early 2000s has been reported in many countries.[10,11] However, little is known about the more recent changes in the prescription pattern of antipsychotics for first-episode schizophrenia after this shift toward increasing SGA use.

Patients with first-episode schizophrenia are more sensitive to a given dose of antipsychotics than chronic

patients.[12] According to a meta-analysis,[13] mean effective doses are up to 50% lower in first-episode schizophrenia than in chronic schizophrenia. However, it is not uncommon for the patients to be given doses that exceed the recommended therapeutic doses.[14,15] Despite consistent recommendations for antipsychotic monotherapy,[7,8,12] the practice of prescribing multiple antipsychotic drugs appears to be increasing,[11] and an association between antipsychotic polypharmacy and high doses of prescribed antipsychotics has been observed.[16,17] Although the use of high-dose prescription and polypharmacy has been studied in chronic patients with schizophrenia, relatively few studies have investigated these treatment strategies in the early stages of the disease.

The present study aimed (1) to examine changes in the prescribing patterns of antipsychotics and other psychotropic drugs between 2005 and 2010, and (2) to identify the relationships among dosage, antipsychotic polypharmacy, and other clinical correlates in patients with first-episode schizophrenia who were discharged from a university psychiatric hospital.

METHODS

Study Settings

This study was carried out at Severance Mental Health Hospital, a locked psychiatric inpatient facility located near Seoul and a part of the Unit of Psychiatry in Yonsei University Health System (YUHS). This residency-affiliated facility admits patients transferred from two other YUHS outpatient units in Seoul and several other mental health centers throughout the country, offering short- to medium-term care for patients with acute and subacute psychiatric conditions. This study was approved by the Institutional Review Board of Severance Mental Health Hospital.

Data Source and Study Population

Data specified according to protocol were collected retrospectively from patient medical records by manual search. Available medical records of all patients with a diagnosis of schizophrenia or schizophreniform disorder (the Diagnostic and Statistical Manual of Mental Disorders 4th edition, text revision [DSM-IV-TR])[18] who were discharged from the hospital between January 1, 2005 and December 31, 2010 were analyzed. We excluded data from patients who had a prior history of psychotic episodes before the most recent episode leading to admission. The year 2005 was chosen as most major atypical anti-

psychotics (including aripiprazole, which was approved by the Korea Food and Drug Administration [KFDA] for the treatment of schizophrenia in 2004) had become commercialized by 2005 in Korea. The year 2010 was chosen as it was the most recent year from which all medical records were available at the time of investigation.

Patient medical records were checked for disease-specific information (length of stay, voluntary or involuntary treatment) and demographic data (such as sex, age, and socioeconomic status). Comprehensive medication profiles included antipsychotics, mood stabilizers, antidepressants, and benzodiazepines. "As needed" medication prescriptions were excluded from consideration. The prescription status of psychotropic drugs at the time of discharge was chosen for analysis. We defined antipsychotic polypharmacy as the concurrent receipt of two or more chemically distinct antipsychotic drugs for at least 14 days. A wide time window of at least 14 days and the prescription status at the time of discharge (after the patient was mostly stable) were utilized to help reduce overestimation of polypharmacy.

Data Analysis

To compare doses of different drugs, the prescribed daily dose (PDD) was divided by the defined daily dose (DDD) to yield a PDD/DDD ratio. DDD is the international unit approved by the World Health Organization for drug use studies[19] and is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults." A PDD/DDD ratio was then calculated as the sum of the individual PDD/DDD ratios of all antipsychotics prescribed to each determinate patient. To maintain consistency with previous studies,[16,17] a high dose was defined as a PDD/DDD ratio of greater than 1.5.

Continuous variables were analyzed parametrically using t-tests. The chi-squared test was used to compare percentages of discrete variables, and Fisher's exact test was used whenever appropriate. Logistic regression analysis was used to adjust for relevant covariates and to identify factors associated with high-dose antipsychotic prescriptions. Initially, potential variables associated with high-dose antipsychotic prescriptions (age, sex, length of hospital stay, socioeconomic status, anticholinergics, antidepressants, antipsychotics polypharmacy, benzodiazepines, mood stabilizers, and year of institutionalization) were selected based on the results of prior studies.[14,20] After univariate logistic regression, only factors with a significance of $p < 0.20$ (age, sex, socioeconomic status, mood stabilizer use, typical antipsychotics use, anti-

Table 1. Sociodemographic and clinical characteristics of individuals diagnosed with schizophrenia for the first time in 2005 and 2010

Variable	2005 (n=47)	2010 (n=52)	χ^2/t	p value
Age (yr)	35.3±12.6	32.5±12.9	1.096	0.276
Sex				
Male	15 (31.9)	17 (32.7)	0.007	0.934
Female	32 (68.1)	35 (67.3)		
Education (yr)	13.3±2.4	14.2±2.5	−1.805	0.074
Social economic status				
Professional	0 (0)	4 (9.3)	6.912	0.141
Intermediate	8 (17.0)	6 (14.0)		
Skilled non-manual/manual	26 (55.3)	27 (62.8)		
Semi-skilled manual	10 (21.3)	4 (9.3)		
Unskilled manual	3 (6.4)	2 (4.7)		
Schizophrenia diagnostic subtype			1.35	0.717
Paranoid	34 (72)	38 (72.7)		
Disorganized	1 (2.1)	2 (3.0)		
Catatonic	0 (0)	1 (1)		
Undifferentiated or schizophreniform disorder	12 (25.5)	11 (23.2)		
Length of hospital stay (day)	55.6±55.5	46.1±27.3	1.088	0.279
Admission method				
Voluntary	1 (2.1)	15 (29.4)	13.328	<0.001
Involuntary	46 (97.9)	36 (70.6)		

Values are presented as mean±standard deviation or number (%).
t=t-test; χ^2=chi-square test.

psychotic polypharmacy, and year of institutionalization) were inserted into the second logistic regression analysis. The Hosmer-Lemeshow goodness-of-fit test was used to assess the overall fit of the logistic regression model. All tests were two-tailed. Statistical analyses were carried out using the PASW Statistics software, ver. 18.0 (IBM Co., Armonk, NY, USA), and differences of $p<0.05$ were considered significant.

RESULTS

Subjects

For this study, 47 and 52 newly treated patients with schizophrenia were enrolled in 2005 and 2010, respectively. Patient demographic and clinical characteristics are shown in Table 1. There were no differences in the 2005 and 2010 patient groups in terms of sex, age, educational level, socioeconomic status, diagnostic subtype of schizophrenia, or length of hospital stay. The rate of involuntary admissions decreased from 97.9% in 2005 to 70.6% in 2010 (χ^2=13.328; $p<0.001$).

First−prescribed Antipsychotic Medication

Fig. 1 shows the first antipsychotic drug obtained from the pharmacy after schizophrenia diagnosis. In 2005, the four most common first-prescribed antipsychotics were olanzapine (34.0%), risperidone (34.0%), aripiprazole (23.0%), and haloperidol (19.1%). In 2009, a new atypical
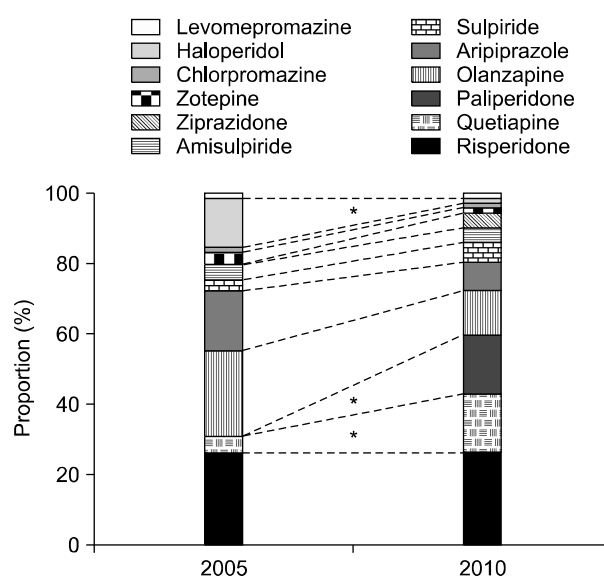

Fig. 1. Proportion of the antipsychotic drug first prescribed after initial schizophrenia diagnosis in 2005 and 2010 (*$p<0.05$).

antipsychotic drug, "paliperidone," was introduced after KFDA approval for the treatment of schizophrenia. In 2010, the list of commonly prescribed antipsychotics changed to risperidone (36.5%), quetiapine (23.1%), paliperidone (23.1%), and olanzapine (17.3%). There were no significant changes in the prescription of FGAs (levomepromazine, chlorpromazine), zotepine, risperidone, olanzapine, clozapine, and amisulpride from 2005 to 2010

Table 2. Distribution of psychotropic drugs use in patients diagnosed in 2005 and 2010

Treatment	2005 (n=47)	2010 (n=52)	χ^2	p value*
High dose of antipsychotics	29 (61.7)	28 (53.8)	0.624	0.430
Antipsychotic polypharmacy	16 (34.0)	18 (34.6)	0.004	0.952
1st generation antipsychotics	12 (25.5)	7 (13.5)	2.319	0.128
2nd generation antipsychotics	46 (97.9)	52 (100)	-	0.475[†]
Anticholinergics	25 (53.2)	27 (51.9)	0.016	0.900
Antidepressants	3 (6.4)	4 (7.7)	-	0.800[†]
Benzodiazepines	30 (63.8)	27 (51.9)	2.564	0.278
Mood stabilizers	0 (0.0)	9 (17.3)	-	0.003[†]

Values are presented as number (%).
*p value on the basis of chi-square test (χ^2) or [†]Fisher's exact test.

Table 3. Factors associated with high-dose antipsychotic prescription (combined data from 2005 and 2010)

Factors	p value	Odds ratio	95% confidence interval
Young age (<35 yr)	0.335	1.766	0.556-5.608
Sex (male)	0.321	1.840	0.552-6.133
Low socioeconomic status	0.326	2.071	0.484-8.865
Mood stabilizer use	0.817	1.306	0.136-12.552
Number of typical antipsychotics use	0.656	1.777	0.142-22.251
Antipsychotic polypharmacy	0.008	23.965	2.313-248.332
Year of institutionalization (2005)	0.875	1.102	0.329-3.695

(Fig. 1). However, the rate of haloperidol prescription decreased from 19.1% in 2005 to 1.9% in 2010 (Fisher's exact test; p=0.006), and the rate of quetiapine prescription increased from 6.2% in 2005 to 27.4% in 2010 (χ^2= 31.434; p<0.001).

Prescription of Psychotropic Medications

The practice of antipsychotic polypharmacy and high dose of antipsychotics was similar in 2005 and 2010. A total of 61.7% and 53.8% patients were prescribed high doses of antipsychotics in 2005 and 2010, respectively (Table 2), and 34.6% and 34.0% of patients were prescribed with antipsychotic polypharmacy in 2005 and 2010, respectively. The most frequently prescribed drug within the antipsychotics combinations changed from haloperidol in 2005 (50.0%) to quetiapine in 2010 (50.0%). Prescription of FGAs and SGAs were not significantly different between these years. Prescription of anticholinergics, antidepressants, and benzodiazepines was unchanged between 2005 and 2010; however, prescription of mood stabilizers increased from 0.0% in 2005 to 17.3% in 2010 (Fisher's exact test; p=0.003).

Factors Associated with High Doses of Antipsychotics

Prescription of high-dose antipsychotics was not asso-

ciated with patient age, sex, socioeconomic status, mood stabilizer use, typical antipsychotics use, or year of institutionalization (Table 3). Antipsychotic polypharmacy was most strongly associated with high doses of antipsychotics (odds ratio=23.965; 95% confidence interval 2.313-248.332; p=0.008). According to the Hosmer-Lemeshow goodness-of-fit statistics, the reliability of the model was adequate (χ^2=3.645; p=0.373).

DISCUSSION

The purpose of this study was to describe prescription trends for antipsychotics use and related drugs in patients with first-episode schizophrenia by comparing prescribed medications between the years of 2005 and 2010. In the present study, the overall rate of high-dose antipsychotic prescription during the initial inpatient treatment of first-episode schizophrenia was more than 60% in 2005 and was similarly high in 2010. Furthermore, both time points showed antipsychotic polypharmacy rates of more than 34%, and polypharmacy was strongly associated with high-dose prescriptions after controlling for other clinical variables.

Many reasons may explain the intensified treatments of high-dose antipsychotics in addition to antipsychotic polypharmacy, despite little scientific evidence to support these treatments. Increasing the dosage and combining different antipsychotics is one of several options that may be chosen when the response to initial prescriptions is insufficient, and high-dose prescriptions may initially be applied if assuming an accelerated response. Furthermore, psychiatrists may begin to prescribe higher doses of SGAs even for initial treatment in first-episode psychosis due to experiences with SGAs causing less-pronounced dose-dependent EPS.[21]

Although no high-quality scientific evidence proves that high-dose therapy is beneficial,[22-24] higher doses of

SGAs may be justified in certain cases, as they may improve psychotic symptoms and optimize D_2 receptor blockade if they are titrated close to the peak of their daily dose range.[25] A recent study[26] shows that high-dose SGAs modestly enhance treatment response and should be considered a viable treatment option for first-episode schizophrenia patients. This may contribute to the use of higher doses overall, particularly in individuals who have been prescribed multiple SGAs. However, the titration of antipsychotic doses should be carefully considered based on relevant clinical characteristics of individual patients due to the uncertain consequences of high-dose therapy.

Our findings suggest that SGAs (97.9% in 2005 and 100% in 2010) have rapidly displaced the older first-generation neuroleptics in the initial treatment of schizophrenia in Korea more so than in other countries.[21,27,28] According to a recent comprehensive meta-analysis,[29] several SGAs were shown to have a significantly lower treatment discontinuation than FGAs in first-episode schizophrenia patients irrespective of cause, negative symptoms, and global cognition, despite SGAs causing more weight gain. Although SGAs are preferred in treatment recommendations, convincing evidence of an efficacy difference between FGAs and SGAs in treating a first episode of psychosis is still lacking.[30] While most studies are *post hoc*, SGAs studies are often industry-sponsored and tend to have a subtle bias against FGAs in total symptom reduction and response rate.[29] According to an update by the National Institute for Health and Clinical Excellence, treatment guidelines are beginning to move away from previous recommendations of SGAs as the first-line drugs in patients with first-episode psychosis.[31] Thus, the choice of antipsychotic drug in new-onset schizophrenia treatment may be influenced more by the drug's side-effect profile than its efficacy.[32]

In the present study, olanzapine was the most commonly prescribed initial antipsychotic medication in 2005, yet it was only the fourth most common in 2010. This change in prescribing pattern may reflect increasing concerns about weight gain and metabolic disturbances, which are the most frequent and harmful long-term side effects of SGAs.[33] Although no data has associated metabolic harm with first-response medication in young schizophrenic patients, all other SGAs except for clozapine are likely less harmful than olanzapine.[34,35] The recently updated Schizophrenia Patient Outcomes Research Team (PORT) guidelines recommended specifically against using olanzapine (or clozapine) as a first-line treatment for first-episode psychosis due to its substantial contribution to weight gain and metabolic abnormalities.[36]

Our data showed that the most frequently prescribed drug within antipsychotic combinations changed from haloperidol in 2005 (50.0%) to quetiapine in 2010 (50.0%). This finding is consistent with the recent trend of quetiapine as the most frequently co-prescribed drug.[21,37,38] Furthermore, 78.8% of quetiapine prescriptions in combination with other antipsychotics were at doses of lower than 300 mg/day. This may indicate in part that the drug's compounds were often used in conjunction with other antipsychotics as a potent sedative,[39] rather than its antipsychotic properties. However, a recent meta-analysis warns that patients with schizophrenia are particularly sensitive to quetiapine-induced metabolic abnormalities, even at low doses.[40] Therefore, a prudent approach to prescription and careful monitoring of metabolic side effects is needed when using this antipsychotic to manage first-episode schizophrenia.

The introduction of new compounds for treating psychoses may affect the choice of the first antipsychotic drug after being diagnosed with schizophrenia. In our findings, paliperidone, an atypical antipsychotic medication that was newly approved in 2009, was the second most frequently prescribed drug in 2010. Similarly, the use of aripiprazole, which had been commercialized in Korea after KFDA approval in 2004, was high in 2005 (23%, third most commonly used drug) and decreased to 11.5% in 2010. Whereas the prescribing rate of olanzapine decreased substantially over a 5-year period, the use of risperidone was not strongly influenced by the introduction of new antipsychotics and remained relatively steady. Consistent with our findings, olanzapine use decreased and risperidone use remained steady in a 10-year cohort study of newly diagnosed patients with schizophrenia as newly developed antipsychotics were introduced.[21] Intensive marketing of new antipsychotics by the pharmaceutical companies may have influenced the observed prescription rate trends,[41] and physicians may be more likely to try something new in hopes of maximizing outcomes.

Clozapine has been shown to have advantages over other antipsychotics in terms of efficacy[42] and effectiveness[43], with comparable cost-effectiveness to that accepted for many medical interventions.[44] However, in spite of the clinical guidelines, clozapine is used less and later than recommended, as shown in our findings. Moreover, recent studies[45,46] indicate that the incidence and mortality of clozapine-induced agranulocytosis, the most feared side effect, could be lower than previously estimated. Another

cohort study[47] reported that all-cause mortality due to clozapine is substantially inferior to that associated with other antipsychotic drugs and recommended that the restrictions regarding the use of the drug be reevaluated. Although few studies have been carried out, randomized clinical trials with clozapine in treating first psychotic episodes have supported the superiority of clozapine over other antipsychotics.[48,49] Therefore, clozapine should be considered when choosing antipsychotics for the early treatment of first-episode schizophrenic patients, especially in cases of non-response.[50]

Although our data came from patients with non-affective and first-episode schizophrenia, we found a significant increase in the prescription of mood stabilizers from 2005 to 2010, which is consistent with the increase in the prescription of mood stabilizers in other studies of first-episode psychosis.[21,28] The increased use of mood stabilizers may be due to evidence implicating mood disturbances in the disease burden and prognosis of schizophrenic patients.[51] The mood stabilizers may be used in conjunction with antipsychotics to control agitation and violence in the acute psychotic state.[52] This intensified conjunctive therapy may be partly attributable to secular trends in the structure and delivery of psychiatric services (i.e., the general shift to voluntary psychiatric hospitalization or outpatient care). The revised mental health legislation in Korea that took effect on March 22, 2009 limits involuntary admission through more stringent admission procedures, which may have influenced the significant decrease in the involuntary admission rate we observed between 2005 and 2010. Under voluntary admission, rapid tranquilization may be required using more active psychopharmacological approaches.

Several limitations of our study warrant consideration. First, although data were collected prospectively as part of the principal investigator's regular clinical duties, our investigation was limited to a retrospective review methodology. Second, we lacked information regarding illness severity and drug tolerability. Third, we performed our investigation at only a single residency-affiliated inpatient facility that carried more acute unstable patients with higher rates of involuntary admission, which may have biased the results toward higher-than-normal rates of high-dose prescriptions. Additionally, the small sample size of this study limits the generalizability of our findings. Finally, our observed rate of high-dose antipsychotic prescription could be somewhat overestimated. DDD, defined as the assumed average dose per day for maintenance treatment,[19] has been criticized for promoting subtherapeutic doses in the treatment of psychosis.[53] Therefore, PDD/DDD ratios may be higher for stabilized patients immediately after hospital discharge than for outpatients during the maintenance phase.

The prescription of high-dose antipsychotics with antipsychotic polypharmacy is a common clinical practice for treating patients with chronic schizophrenia. This study investigating the initial treatment of first-episode schizophrenia showed that the rates of excessive dosing were high in both 2005 and 2010, as more than one-third of patients received two or more antipsychotic agents in both years and antipsychotic polypharmacy was the main factor associated with high-dose antipsychotics use. However, the most common types of antipsychotics prescribed were different between the two years, and the use of mood stabilizers significantly increased for non-affective schizophrenia in 2010. Further prospective studies are needed to determine the optimal dosages of antipsychotics and the effects of concomitant medications during the early stage of psychosis.

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