OPEN

Antipsychotic Polypharmacy Is Associated With Adverse Drug Events in Psychiatric Inpatients

The Japan Adverse Drug Events Study

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Abstract:

Background: Antipsychotic (AP) polypharmacy (APP), the coprescription of more than 1 AP, is frequently practiced in psychiatric inpatients and is considered to be a risk factor for adverse drug events (ADEs). However, the association between APP and ADEs among psychiatric inpatients has not been well investigated.

Methods: The Japan Adverse Drug Events (JADE) study was a series of cohort studies conducted in several clinical settings. In particular, the JADE study for psychiatric inpatients was a retrospective cohort study of 448 psychiatric inpatients with a cumulative 22,733 patient-days. We investigated the relationship between APP, defined as a concurrent prescription of 2 or more APs and ADEs. We also assessed the relationship between potential risk factors for ADEs due to APs.

Results: Among the 448 patients included in this study, 106 patients (24%) had APP and the remaining 342 patients were prescribed 1 AP or none. Risperidone was the most frequent drug (25%, 109/442 AP prescriptions) used, and levomepromazine was most frequently prescribed as a concurrent medication with other APs (91%, 29/32). The median number of ADEs among the patients with APP was significantly higher than in those without APP ($P = 0.001$). Antipsychotic polypharmacy was a risk factor for the occurrence of first (adjusted hazard ratio, 1.54; 95% confidence interval, 1.15–2.04) and second (adjusted hazard ratio, 1.99; 95% confidence interval, 1.40–2.79) ADEs.

Conclusions: Antipsychotic polypharmacy was a risk factor for the occurrence of single and multiple ADEs. Antipsychotic polypharmacy should be conservatively and minimally practiced.

Key Words: adverse drug events, antipsychotic polypharmacy, epidemiology, psychiatry, patient safety

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Received January 7, 2021; accepted after revision March 14, 2021.

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N.A. received grants from the Pfizer Health Research Foundation (13-9-004) and the Osaka Medical Research Foundation for Intractable Diseases (28-2-1); however, the funding sources had no further role in the preparation, data collection, or writing of this manuscript. The other authors declare no conflicts of interest.

ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000001416

(*J Clin Psychopharmacol* 2021;41: 397–402)

Polypharmacy is the concurrent use of multiple medications in 1 patient.[1] In practice, polypharmacy prescriptions have ranged from 2 to 11 medications at a time, but the use of 5 or more concurrent medications seems to be the most common definition.[1] In any case, the term polypharmacy often implies the use of more medications than are clinically necessary. For example, in the treatment of hypertension, diabetes, and infections, concurrent use of multiple medications has become a rule rather than the exception, because treating these illnesses sometimes requires the use of multiple medications with varied pharmacodynamic properties.[2,3]

Regarding psychiatric patients, concurrent multiple medications are needed when psychiatric symptoms cannot be treated by a single psychotropic drug because of treatment resistance or the comorbidity of 2 or more psychiatric disorders. For example, combining lithium or second-generation antipsychotics (APs, SGAs) with serotonin reuptake inhibitors for treatment-resistant depression is the recommended treatment in some clinical guidelines.[4,5] Combination therapy is recommended as a second step when monotherapy has not been effective in the treatment of bipolar disorder.[6] It has been reported that approximately 80% of patients with bipolar disorder take 2 or more psychotropic drugs and approximately 40% of them take 4 or more.[7]

Not all use of multiple concurrent medications is inappropriate in a psychiatric setting; however, in many instances, the use of multiple concurrent medications, especially polypharmacy, may place patients at an increased risk for adverse events and poor health outcomes. Specifically, patients experience increased mortality, falls, adverse drug events (ADEs), prolonged hospital stay, and eventually readmission to the hospital after discharge.[8–10]

In psychiatric treatment, APs are frequently used to relieve symptoms of many mental disorders (ie, schizophrenia, bipolar disorder, major depressive disorder, obsessive-compulsive disorder, delirium, and neurodevelopmental disorders), and AP polypharmacy (APP), which is known as the coprescription of more than 1 AP, is frequently seen in clinical psychiatric settings.[11] The reported rate of APP in psychiatric inpatients is approximately 20% to 66% in the world,[11–13] and approximately 55% to 66% of inpatients with schizophrenia received APP in Japan.[11,13–15] Many clinical guidelines recommend AP monotherapy as the treatment of choice[16–18]; however, evidence on the risks and benefits of APP is equivocal, and it is unclear how APP affects the development of ADEs in psychiatric inpatient settings. Thus, we investigated the impact of APP on the occurrence of ADEs among inpatients with psychiatric disorders.

MATERIALS AND METHODS

Study Design and Patient Population

The Japan Adverse Drug Events (JADE) study was a series of cohort studies conducted in several clinical settings.[3,19] The

JADE study for psychiatric inpatients was a retrospective cohort study of 448 psychiatric inpatients, with a cumulative 22,733 patient-days in 2 hospitals, over 1 year.[20] These hospitals included acute care units (main section of a psychiatric department in which patients with an acute mental disorder received targeted care), nursing care units (used by patients who have recovered from the acute stage of their condition but still require nursing care), and medical care units (specialized sections within a psychiatric department that provide treatment to psychiatric patients with physical medical conditions). We considered 1 hospitalization during the study period as 1 patient, regardless of whether it was a readmission or a new hospitalization.

This study was approved by the institutional review board of the Kyoto Prefectural University of Medicine and by the institutional review boards of the 2 participating hospitals. This study was performed according to the regulations set forth in the Declaration of Helsinki.[21] The need for informed consent was waived because all data were collected as part of daily clinical practices.

Definition of ADEs/APP and Data Collection Process

In accordance with previous studies, an ADE was defined as any injury caused by medication use, irrespective of medication errors,[3,22] and the data regarding the ADE were collected through a review process that was previously reported.[22] Four psychiatrists and 2 physicians reviewed all the medical charts, along with laboratory reports, incident reports, and prescription queries from all psychiatric inpatients who were admitted to and discharged from the acute, nursing, and medical care units between April 1, 2010, and March 31, 2011. They collected administrative data, including details of the medications based on each patient's medical condition. Comorbidity in the patients was quantified using the Charlson Comorbidity Index.[23] Psychiatrists and physicians identified ADEs and collected medication details that were related to the ADE, including the name, dose, route of administration, and class of medication.

Once all the data were collected from the participating hospitals, the reviewers independently classified relevant incidents as an ADE or an exclusion. All determinations were based on the Naranjo algorithm, the established scale for determining the likelihood of whether an ADE was caused by a particular medication, as well as on published reports that showed an association between a particular medication and an ADE.[22] The reviewers also independently classified all incidents into the following categories, according to their severity: fatal, life-threatening, serious, and significant. Fatal ADEs were those that resulted in death. Life-threatening ADEs were those that caused issues, such as respiratory depression or suicidal behavior. Serious ADEs included gastrointestinal bleeding, falls, or a decrease in blood pressure. Significant ADEs included cases with milder symptoms, such as constipation, diarrhea, extrapyramidal symptoms, or oversedation.

After all suspected incidents were collected, the reviewers met to confirm the final classification for each incident. When the reviewers disagreed on the classification of an incident, they reached a consensus through discussion. We calculated interrater reliability using k-statistics. κ score between reviewers regarding the presence of an ADE was 0.96 (ADE vs potential ADE or exclusion). The κ score for severity was 0.43 (significant vs serious or life-threatening).[20] These values were similar to those reported in previous studies.[3,24]

We classified the medications into 25 categories (including 12 classes of psychotropic drugs) as follows: sedatives (benzodiazepine receptor agonist), sedatives (others), anxiolytics, antidepressants (selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, noradrenergic and specific serotonergic antidepressant), antidepressants (others), mood stabilizers, stimulants, SGAs, first-generation APs, anticonvulsants, anti-parkinsonian drugs and antidementia medications. We defined APP as 2 or more AP prescriptions taken simultaneously for at least 7 consecutive days, or for all the days of hospital admission, if the duration of stay was shorter than 7 days. We did not take into consideration any medications that were taken on an "as-needed" basis. In addition, we defined the participants receiving APP as the APP group and defined the other participants as the non-APP group, regardless of presence of physical drugs.

Statistical Analyses

Continuous variables are presented as means with standard deviations (SDs) or medians with interquartile ranges (IQRs), and categorical variables are shown as raw scores and percentages.

The relationship between patients' characteristics and APP was assessed using either *t* test or Wilcoxon rank sum test, when

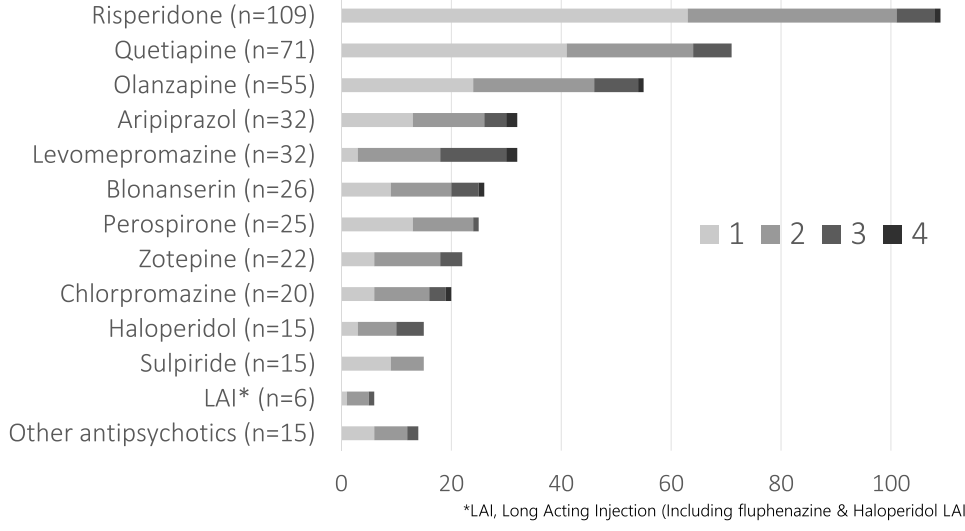


FIGURE 1. Patterns of usage for each AP drug.

a characteristic was a continuous variable, and the χ^2 test or Fisher exact test, when a characteristic was a categorical variable.

The primary unit of analyses was the relationship between APP and ADEs. We compared the median number of ADEs of the APP group with that of the non-APP group, using the Wilcoxon rank sum test. In addition, we conducted survival analyses to compare the 2 groups regarding the time to occurrence of the first and second ADE, plotting Kaplan-Meier survival curves and using the log-rank test. We analyzed the time to the first ADE to compare the occurrence of ADE between the 2 groups. We subsequently analyzed the time to the second ADE to compare multiple occurrences of ADE between the 2 groups.

We also conducted multivariable Cox proportional hazard models to assess the relationship between potential risk factors and occurrence of the first and second ADEs, in the 2 groups. Eight independent variables were included in the Cox proportional hazards analyses: age (0 for younger than 65 years, 1 for 65 years or older), the number of medications being taken upon admission (0 for less than 5, 1 for 5 or more), type of admission (0 for voluntary admission, 1 for involuntary admission), ward type (0 for nursing and medical care unit, 1 for acute care unit), restraint or seclusion upon admission (0 for absent, 1 for present), score on the Carlson Comorbidity Index (0 for less than 5, 1 for 5 or more), history of allergies (0 for absent, 1 for present), systolic blood pressure upon admission (0 for 100 mm Hg or more, 1 for less than 100 mm Hg), and body mass index (BMI) upon admission (0 for 20 or more, 1 for less than 20). All analyses were performed using JMP V.14.0 software (SAS Institute, Cary, NC).

RESULTS

Participant Characteristics and Status of Prescription

Among the 448 patients included in the JADE Study for psychiatric inpatients, 247 (55%) were female and 185 (41%) were 65 years or older. In total, there were 22,733 patient-days, and the median hospital stay was 32 days (IQR, 15–75 days).

Overall, 5570 medications were ordered during the hospital stay for all patients (median, 11; IQR, 7–16) and 3990 regular medications were ordered (median, 8; IQR, 5–12) to 435 patients (97.1%). Among the regular medications, 1769 prescriptions were psychotropic drugs (median, 4; IQR, 2–5) in 402 patients (89.7%). A total of 525 APs (median, 1; IQR, 0–2) were prescribed to 299 patients (66.7%), and of that, 442 were prescribed to 290 patients over the course of 7 days or for the entirety of their stay if the duration of the hospital stay was shorter than 7 days. In continuously prescribed APs, 45% (197/442) were prescribed as monotherapy. Risperidone was the most frequently prescribed AP (25%, 109/442) and also had one of the highest rates of use as a monotherapy (58%, 63/109). On the other hand, levomepromazine was most frequently prescribed as a concurrent medication with other APs (91%, 29/32; Fig. 1).

The number of patients with APP was 106 (23.6%). In the non-APP group, 184 patients (41.1%) received AP monotherapy and 158 (35.3%) were not prescribed APs continuously. In comparison, by patient's main diagnosis, the proportion of psychotic disorder and intellectual/neurodevelopmental disorder in the APP group was significantly higher than that in the non-APP group (58% vs 15%, $P < 0.001$; 25% vs 11%, $P < 0.001$, respectively; Table 1). In contrast, the proportion of mood disorders and organic mental disorder, including dementia, in the APP group was significantly lower than that in the non-APP group (9% vs 23%, $P = 0.002$; 11% vs 34%, $P < 0.001$, respectively).

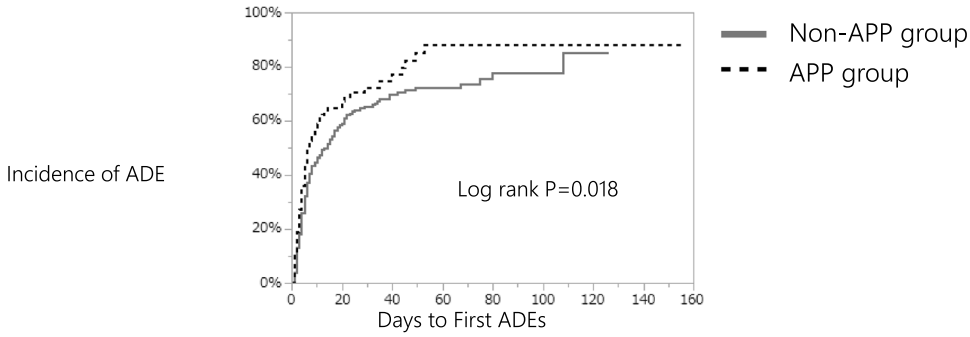
TABLE 1. Demographic Data of the Participants

Factors	APP Group (n = 106)	Non-APP Group (n = 342)	*P*
Female, n (%)	55 (52)	192 (56)	0.44
Age, mean (SD), y	49 (18)	58 (23)	<0.001
Ward type, n (%)			
Acute care unit	94 (89)	247 (72)	<0.001
Nursing care unit	11 (10)	69 (19)	0.04
Medical care unit	1 (1)	31 (9)	0.005
Involuntary admission, n (%)	38 (36)	148 (43)	0.17
Seclusion or restraint, n (%)	12 (11)	28 (8)	0.27
Psychiatric diagnosis, n (%)*			
Psychotic disorders	62 (58)	52 (15)	<0.001
Schizophrenia	49 (46)	44 (13)	<0.001
Other psychotic disorders	13 (12)	8 (2)	<0.001
Mood disorders	10 (9)	79 (23)	0.002
Bipolar affective disorder	7 (7)	29 (8)	0.5
Major depressive disorder	1 (1)	37 (11)	<0.001
Other mood disorders	2 (2)	13 (4)	0.17
Organic mental disorders	12 (11)	115 (34)	0.001
Dementia	10 (9)	102 (30)	<0.001
Other organic mental disorders without dementia	2 (2)	13 (4)	0.18
Intellectual and developmental disabilities	27 (25)	36 (11)	<0.001
Mental retardation	18 (17)	27 (8)	0.004
Developmental disabilities without mental retardation	9 (8)	9 (3)	0.009
Charlson Comorbidity Index, median (IQR)	0 (0–1)	1 (0–2)	<0.001
No. drugs upon admission, median (IQR)			
All drugs	6 (3.75–8)	4 (2.75–7)	0.001
Physical drugs	1 (0–3)	2 (0–5)	0.002
Psychiatric drugs	4 (2–5)	1 (0–3)	<0.001
History of allergy, n (%)	12 (11)	37 (11)	0.88
Systolic blood pressure, mean (SD), mm Hg	132 (21)	129 (23)	0.87
BMI, mean (SD), kg/m^2	25 (5.6)	22 (4.6)	<0.001

*Diagnoses based on the *International Classification of Diseases, Tenth Revision*.[25]

Adverse Drug Events Among APP and Non-APP Group

During the study period, we identified 955 ADEs among 283 patients (63%). The most common class of drugs associated with ADEs was atypical APs (34%, 323/955), followed by typical APs (13%, 125/955), and sedatives including benzodiazepine (8.5%, 81/955). Central nervous system symptoms including fall, oversedation, and extrapyramidal symptoms were the most frequent symptoms (44%, 415/995), followed by gastrointestinal symptoms including diarrhea and constipation (34%, 326/955), allergic or skin symptoms including drip leakage (6%, 58/955),



Days	0	30	60	90
Cumulative incidence		72.2%	88.2%	88.2%
Number of events	0	71	77	77
Number of patients at risk	106	14	4	2

APP group

Days	0	30	60	90
Cumulative incidence		65.2%	72.4%	77.6%
Number of events	0	193	202	205
Number of patients at risk	342	54	26	9

Non-APP group

ADE, Adverse Drug Event; APP, Antipsychotic Polypharmacy

FIGURE 2. Kaplan-Meier survival curves: first ADEs.

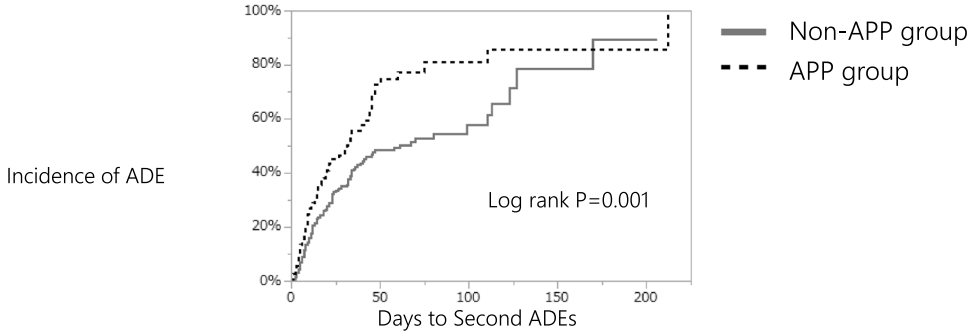
and metabolic or liver dysfunction (5%, 49/955). Constipation (22%, 209/955) was the most frequent symptom, followed by falls (15%, 146/955), extrapyramidal symptoms (10%, 92/995), oversedation (9%, 82/995), and then diarrhea (6%, 53/995). Regarding severity, life-threatening and serious ADEs accounted for 1.4% (13 events in 12 patients) and 28% (265 events in 124 patients) of events, respectively. There were no fatal ADEs that occurred during this study.

The total number of ADEs was 323 (median, 2; IQR, 0–4) in the APP group and 632 (median, 1; IQR, 0–2) in the non-APP group. The median number of ADEs in the APP group was significantly higher than that in the non-APP group ($P = 0.001$). In addition, the proportion of patients in the APP group who experienced serious or life-threatening ADEs was significantly higher than that in the non-APP group (36% vs 26%, $P = 0.0499$). The proportion of only life-threatening events in the APP group (5.8%, 6/106) was significantly higher than that in the non-APP group (1.8%, 6/342, $P = 0.04$).

Figures 2 and 3 depict the time to first and second ADE between the 2 groups on Kaplan-Meier plots, by the presence or absence of APP. The incidence of the first and second ADE in the APP group was significantly higher than that of the non-APP group (log-rank test for equality of survival functions: $P = 0.018$ and 0.001, respectively).

Cox proportional hazard model estimation also showed that the risk of occurrence of the first and second ADE in the APP group was significantly higher than that in the non-APP group (adjusted hazard ratio [HR], 1.54; 95% confidence interval [CI], 1.15–2.04 and HR, 1.99; 95% CI, 1.40–2.79, respectively; Table 2)

In addition, the concurrent use of more than 5 medications (adjusted HR, 1.40 and 1.63; 95% CI, 1.09–1.81 and 1.18–2.25, respectively) and a BMI of less than 20 (adjusted HR, 1.50 and 1.84; 95% CI, 1.16–1.95 and 1.33–2.55, respectively), were also risk factors for the occurrence of a first and second ADE. Furthermore, a higher Charlson Comorbidity Index score was also a risk



Days	0	30	60	90	180
Cumulative incidence		48.2%	77.3%	81.1%	85.8%
Number of events	0	44	58	59	60
Number of patients at risk	106	32	10	5	1

APP group

Days	0	30	60	90	180
Cumulative incidence		35.2%	49.4%	54.5%	89.3%
Number of events	0	95	115	119	125
Number of patients at risk	342	108	51	23	2

Non-APP group

ADE, Adverse Drug Event; APP, Antipsychotic Polypharmacy

FIGURE 3. Kaplan-Meier survival curves: second ADEs.

TABLE 2. Hazard Ratios of APP on the First and Second ADE Occurrence From Cox Proportional Hazards Models

	Crude			Adjusted		
Outcome	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
First ADE	1.36	1.04–1.76	0.02	1.54	1.15–2.04	0.004
Second ADE	1.66	1.21–2.25	0.001	1.99	1.40–2.79	<0.001

factor for the occurrence of second ADE (adjusted HR, 2.37; 95% CI, 1.08–4.65).

DISCUSSION

This study revealed that among psychiatric inpatients in Japan, patients with APP were more likely to develop 1 or more ADEs compared with individuals given AP monotherapy or with those without AP exposure. In patients with schizophrenia, APP increased the frequency of symptoms, such as Parkinsonian symptoms, hyperprolactinemia, hypersalivation, sedation, cognitive impairment, diabetes, and hyperlipidemia, compared with AP monotherapy,[26] although it was unclear how APP affected the occurrence of ADEs. Our comprehensive clinical epidemiological study showed that not only does APP increase the risk of patients having single and multiple ADEs but also patients receiving APP have a higher rate of developing more severe ADEs than patients with AP monotherapy and without AP exposure. A previous study reported that APP increases mortality,[27] although others have reported no effect.[28–30] In our study, we did not find any fatal ADEs; however, the frequency of life-threatening ADEs was significantly higher in the APP group, which may support the notion that APP may be a risk factor for increased mortality.

The reported prevalence of APP in hospitalized patients was approximately 20% to 66%, primarily in individuals with schizophrenia.[11,13,26] Antipsychotic polypharmacy in Asia was reported to be approximately 32% to 40%, whereas in Japan particularly, the rate was as high as 55% to 66%. In our study, APP was observed in 62 (54%) of the 114 patients with psychotic disorder, and the frequency of APP was similar to those reported in previous findings. Patients with schizophrenia were one fourth of all the patients in our study; thus, we examined the proportion of APP in patients with a diagnosis other than schizophrenia. Patients with intellectual/neurodevelopmental disabilities received APP frequently (43%, 27/43), and approximately 10% of patients with mood disorders (11%, 10/89) and organic mental disorders, including dementia (9.4%, 12/127), had also received APP. In a previous study on APP in psychiatric inpatients in Italy, approximately 13% (16/120) of patients with mood disorders received APP, a rate comparable with our study, but the frequency of APP in patients with mental retardation or organic mental disorders was not reported.[31] Antipsychotics, especially SGAs, are prescribed for a wide range of mental disorders, such as bipolar disorder, major depressive disorder, neurodevelopmental disorders, behavioral and psychological symptoms of dementia, and obsessive-compulsive and related disorders, including obsessive-compulsive disorder.[32] In particular, SGAs are often used for sedation when the patient is agitated or excited. Previous studies on APP have focused on patients with schizophrenia; therefore, the outcomes of APP in nonschizophrenic patients are unclear. The results of this survey indicated the APP trends in nonschizophrenic patients. In recent years, several studies, including meta-analysis, have reported that APP, mainly the combination of clozapine with other SGAs, is superior to monotherapy in terms of efficacy.[33] These reports, however, did not assess the risk of adverse events. Antipsychotics will continue to be widely prescribed for various psychiatric disorders; therefore, it is necessary to consider their safety and efficacy.

In addition, more than half of the first and second ADEs developed within 30 days of admission and concurrent use of more than 5 medications (including physical treatment drugs), higher Charlson Comorbidity Index scores, and BMI of less than 20 were associated with the occurrence of multiple ADEs. Therefore, psychiatrists should be considerate about the risk for developing ADEs in patients who have just been hospitalized, are taking multiple drugs, have multiple comorbidities, and are underweight.

Our study has several limitations. First, our study is a historical cohort study performed by review of the patients' medical chart; therefore, some ADEs may have been missed, and some ADEs that had not been described in the medical record could not be evaluated, which would mean that our results underestimate their true incidence. However, we were able to precisely evaluate and collect data on confirmed incidents, especially physical symptoms due to ADEs. Our preciseness was because internists with experience in the classification of ADEs, as a result of previous research on this topic, were used for making proper identification of ADEs.[3,19] In addition, more robust alternatives for measuring ADEs and medication errors have yet to be developed, and the approach that we used in this study is the most commonly used, suggesting that the approximations obtained herein are currently the most accurate. Second, our study only evaluated the risk of ADE based on the number of concomitant APs and did not evaluate the dose of APs and concomitant medication, such as anticholinergic drugs. The results of this study suggest that a large dosage of combined APP promotes a higher risk of ADE occurrence than a small dosage; this is mainly due to the fact that an increase in the number of drugs used is inevitably accompanied by an increase in dosage, thus increasing exposure. However, further studies are needed to more accurately assess the influence of total daily APP dosage and concomitant medication on ADE occurrence. Third, our definition of APP included different patterns of APP: cross-titration during switch between APs and relatively persistent polypharmacy. Antipsychotic polypharmacy caused by cross-titration is frequently seen in clinical practice; therefore, further studies are needed to investigate the relationship between APP type (cross-titration or relatively persistent polypharmacy) and occurrence of ADEs. Finally, most ADEs in our study were at a significant level in our severity category. To investigate the influence of APP on more severe ADEs, larger studies need to be performed with an increased number of patients.

In conclusion, APP was common, and one fourth of psychiatric inpatients received APP. Antipsychotic polypharmacy was significantly associated with the occurrence of ADE. Thus, APP should be avoided as much as possible, except for specific indications for APP, and psychiatrists should carefully monitor for the occurrence of ADEs when APP is required. In addition, APs will continue to be widely prescribed for various mental disorders; therefore, it is necessary to consider the safety and efficacy. We believe that the importance of epidemiological investigations regarding safety in clinical settings, such as our study, will continue to grow in the future.

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