Objective: The aim of this study was to survey the use of antipsychotic polypharmacy (APP) in older Asian patients with schizophrenia and examine its demographic and clinical correlates.

Methods: Information on hospitalized patients with schizophrenia aged 55 or older was extracted from the database of the Research on Asian Psychotropic Prescription Patterns study. Data on 1439 patients in 6 Asian countries and territories including China, Hong Kong, Japan, Korea, Singapore, and Taiwan were analyzed. Sociodemographic and clinical characteristics and antipsychotic prescriptions were recorded using a standardized protocol and data collection procedure.

Results: The frequency of APP prescription was 51.6% in the pooled sample with wide intercountry variations. Multiple logistic regression analysis of the whole sample showed that patients on APP had higher antipsychotic doses and also were more likely to receive first-generation antipsychotics.

Conclusions: Use of APP was common in older Asian patients with schizophrenia. Given the limited evidence supporting its efficacy, the potentially severe side effects and high costs, APP should be used with caution in this population. The reasons for and outcomes of the use of APP in this patient population merit further exploration.

Key Words: schizophrenia, prescription patterns, antipsychotic polypharmacy, psychogeriatric patients, Asia

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and October 2008 to March 2009 using the same design and standardized protocol. Consensus meetings on data collection and uniformity of data entry were held before each survey. The participating countries and territories include mainland China (China hereafter), Hong Kong, Japan, Korea, Singapore, and Taiwan. Centers in India, Malaysia, and Thailand joined the surveys in 2009. Details of the REAP project have been described elsewhere.13,14

Patients were enrolled in this study if they met the following criteria: (1) International Statistical Classification of Diseases, 10th Revision or Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition schizophrenia; (2) age of 55 years or older; (3) taking antipsychotic drugs; and (4) ability to understand the study aims. Patients having major medical conditions were excluded. Doses of antipsychotic drugs were converted into chlorpromazine equivalent milligrams,15-17 and the total dose of antipsychotics is the sum of every antipsychotic drug.

Eligible patients were recruited consecutively, and their sociodemographic and clinical characteristics including age, sex, length of illness, type and doses of antipsychotics, presence or absence of significant psychotic symptoms in the past month, and extrapyramidal adverse effects (EPS) were collected by a review of medical records in 2001 and by either a review of medical records only or a review of medical records supplemented by a patient interview in 2004 and 2009 using a questionnaire designed for the study. Tardive dyskinesia is treated separately from the other forms of EPS because of its phenomenological and treatment characteristics. The data were collected by the attending psychiatrists or by members of the research team with the agreement of the psychiatrist in charge of the patient.

The study was approved by the clinical research ethics committee of the respective centers. Given the anonymous nature of this observational study and minimal risk to patients, the patients' informed consent was exempted in some participating study sites according to the requirements of the local clinical research ethics committee if only a review of case notes was used. All patients receiving the interview provided written or oral consent according to the requirements of the clinical research ethics committee in the respective study sites. The requirements of the clinical research ethics committee usually vary on a local basis across different study sites.

**Statistical Analysis**

The data were analyzed using Statistical Package for the Social Sciences version 13.0 for Windows. Comparisons between the 3 surveys with respect to APP prescribing patterns were made with $\chi^2$ tests. Multiple logistic regression analysis with the “Enter” method was used to determine the demographic and clinical variables influencing APP. Cross-sectional APP use was the dependent variable, whereas independent variables included study sites and time, age, sex, psychopathology, length of illness, use of first-generation antipsychotics (FGAs), dose of antipsychotics, and the presence of EPS and tardive dyskinesia. The level of significance was set at $P = 0.05$ (2-tailed).

**RESULTS**

Altogether, 31 psychiatric institutions were involved in 2001, 25 in 2004, and 50 in 2009. A total of 6761 patients participated in the 3 arms of the REAP study: 2399, 2136, and 2226 patients in 2001, 2004, and 2009, respectively. Of them, 1452 patients satisfied the study criteria. There were only 5 patients in India and 8 patients in Malaysia, the patients in these 2 sites were not included in the analyses. Finally, 1439 patients were included in this study: 490 patients in 2001, 446 patients in 2004, and 503 in 2009. A total of 742 patients of the 1439 patients received APP (51.7%) in the 3 REAP surveys: 286 (58.4%) in 2001, 218 (48.9%) in 2004, and 238 (47.3%) in 2009. There was a significant difference among the 3 surveys in use of APP ($\chi^2 = 14.0, df = 2, P = 0.001$). Table 1 presents the sociodemographic and clinical characteristics of the whole sample and separately for patients by study site. Figure 1 shows


<table>
<thead>
<tr>
<th></th>
<th>China (n = 215)</th>
<th>Hong Kong (n = 43)</th>
<th>Japan (n = 826)</th>
<th>Korea (n = 128)</th>
<th>Singapore (n = 84)</th>
<th>Taiwan (n = 143)</th>
<th>Total (n = 1439)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>59.5</td>
<td>53.3</td>
<td>62.7</td>
<td>6.4</td>
<td>64.2</td>
<td>6.8</td>
<td>59.8</td>
</tr>
<tr>
<td>SD</td>
<td>5.3</td>
<td></td>
<td>6.4</td>
<td></td>
<td>4.5</td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td>CPZeq, mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>431</td>
<td>334</td>
<td>404</td>
<td>379</td>
<td>636</td>
<td>616</td>
<td>577</td>
</tr>
<tr>
<td>%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>19</td>
<td>8.8</td>
<td>3</td>
<td>7.0</td>
<td>16</td>
<td>1.9</td>
<td>5</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of illness &lt;5 y</td>
<td>114</td>
<td>53.0</td>
<td>23</td>
<td>53.5</td>
<td>436</td>
<td>52.8</td>
<td>54</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>116</td>
<td>54.0</td>
<td>25</td>
<td>58.1</td>
<td>562</td>
<td>68.0</td>
<td>90</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>151</td>
<td>70.2</td>
<td>28</td>
<td>65.1</td>
<td>597</td>
<td>72.3</td>
<td>64</td>
</tr>
<tr>
<td>EPS</td>
<td>32</td>
<td>14.9</td>
<td>24</td>
<td>55.8</td>
<td>270</td>
<td>32.7</td>
<td>38</td>
</tr>
<tr>
<td>TD</td>
<td>13</td>
<td>6.0</td>
<td>11</td>
<td>25.6</td>
<td>74</td>
<td>9.0</td>
<td>6</td>
</tr>
<tr>
<td>FGA</td>
<td>82</td>
<td>38.1</td>
<td>19</td>
<td>44.2</td>
<td>588</td>
<td>71.2</td>
<td>89</td>
</tr>
<tr>
<td>SGA</td>
<td>161</td>
<td>74.9</td>
<td>22</td>
<td>51.2</td>
<td>513</td>
<td>62.1</td>
<td>61</td>
</tr>
<tr>
<td>APP</td>
<td>58</td>
<td>27.0</td>
<td>18</td>
<td>41.9</td>
<td>544</td>
<td>65.9</td>
<td>46</td>
</tr>
</tbody>
</table>

*There were no older patients in Thailand.
†Any use of FGA.
‡Any use of SGA.
APP indicates Antipsychotics polypharmacy; CPZeq, chlorpromazine equivalents; EPS, extrapyramidal symptoms; FGA, first-generation antipsychotic; TD, tardive dyskinesia; SGA, second-generation antipsychotic.
the use of APP in participating countries and regions over the study period.

Table 2 displays the prescribing patterns of antipsychotic drugs prescribed in the 3 surveys. The combination of FGAs decreased, whereas the combinations of second-generation antipsychotics (SGAs) and those of FGAs and SGAs increased over time. Table 3 presents the factors that were independently associated with APP. Patients on APP had a higher dose of antipsychotics and were more likely to receive FGAs than those prescribed antipsychotic monotherapy.

### DISCUSSION

To the best of our knowledge, this was the first international study investigating the use of APP in older Asian patients with schizophrenia. The hypothesis that only a small proportion of older patients with schizophrenia would receive APP was not supported. Surprisingly, 51.6% of the patients were prescribed APP, a figure significantly higher than the 10% to 30% for Western patients with schizophrenia.11,12 Our result is also considerably higher than earlier findings in Asia.19,20 For example, in a random sample of 398 Chinese schizophrenic outpatients aged between 18 and 60 years, 17.6% were on APP.19 There was considerable variation in APP prescription in different study sites varying from 17.5% in Taiwan to 65.9% in Japan.

There are 2 possible reasons for the common use of APP in Asian countries. First, inpatients usually present with more severe symptoms and are more likely to be treatment resistant, which could increase APP use. Second, there is a widely held belief in Asian countries that a combination of medications with different pharmacological components is more effective.21 It should be noted that there is only weak evidence at best supporting improved efficacy with APP, whereas it could increase adverse effects, mortality, and cost of treatment and reduce treatment adherence.22–24 Therefore, strategies recommended by treatment guidelines consistently discourage APP.8,9,25 Considering the higher prevalence of somatic comorbidity in elderly patients with schizophrenia resulting in frequent use of concomitant medications and also the age-related reduced drug clearance of antipsychotics and decreased dopamine receptor reserve,7,26,27 APP should be used sparingly in this patient population. Taken together, the rationale of the common use of APP in older Asian patients with schizophrenia should be reexamined.

Recent studies suggest that physical and psychosocial factors influence treatment response in later life; therefore, both the drug industry and researchers need to further clarify the impact of old age on pharmacologic properties of psychotropic

### Table 3. Demographic and Clinical Correlates Associated With Antipsychotic Polypharmacy in the Combined Sample (n = 1439)

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.2</td>
<td>1.0</td>
<td>0.96–1.01</td>
</tr>
<tr>
<td>Antipsychotic dose, CPZeq, mg/d</td>
<td>&lt;0.001</td>
<td>1.003</td>
<td>1.002–1.003</td>
</tr>
<tr>
<td>Length of illness</td>
<td>0.8</td>
<td>0.9</td>
<td>0.4–1.9</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.2</td>
<td>1.2</td>
<td>0.9–1.6</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>0.8</td>
<td>1.0</td>
<td>0.8–1.4</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>0.99</td>
<td>1.0</td>
<td>0.7–1.4</td>
</tr>
<tr>
<td>EPS</td>
<td>0.9</td>
<td>1.0</td>
<td>0.7–1.4</td>
</tr>
<tr>
<td>TD</td>
<td>0.2</td>
<td>0.7</td>
<td>0.4–1.2</td>
</tr>
<tr>
<td>FGAs</td>
<td>&lt;0.001</td>
<td>10.9</td>
<td>7.8–15.4</td>
</tr>
</tbody>
</table>

Study sites

- China: – 1.0
- Hong Kong: 0.005 3.2 1.4–7.1
- Japan: <0.001 3.9 2.5–5.9
- Korea: 0.03 0.5 0.3–0.95
- Singapore: 0.002 2.8 1.5–5.5
- Taiwan: 0.005 0.4 0.2–0.8

Study time

- 2001 survey: – 1.0
- 2004 survey: 0.2 1.3 0.9–1.8
- 2009 survey: <0.001 2.0 1.4–3.0

Multiple logistic regression analysis with antipsychotic monotherapy as the reference group.

Centers in India, Malaysia, and Thailand joined the survey in 2009; therefore, they were not included in multiple logistic regression analysis. There was colinearity between the use of FGA and SGA; therefore, the use of SGA was not included in multiple logistic regression analysis.
drugs and enact treatment guidelines for this population. A recent study found that most patients with schizophrenia on APP, even those with persistent psychotic symptoms, tolerated well the switch from APP to AMP, thereby reducing weight gain and EPS. These data support prescribing guidelines that encourage trials of AMP for patients receiving APP.

In this study, the frequencies of APP were comparable across the 3 surveys (58.4%, 48.9%, and 47.7% in 2001, 2004, and 2009), but the proportion of APP involving SGAs (FGAs + SGAs, or SGAs + SGAs) increased over time. The shift toward more APP involving SGAs (FGAs + SGAs, or SGAs + SGAs) over the past 9 years may be driven by the assumed favorable effects on refractory symptoms, lower risk of EPS, and the declining costs of SGAs. However, recent studies failed to find significant difference between FGAs and SGAs in efficacy; at the same time, some SGAs increase the risk of diabetes mellitus, cause weight gain and metabolic syndrome, and add substantial costs to the treatment.

In line with a recent study, a multivariate analysis showed that patients on APP had higher doses of antipsychotics. More frequent use of FGAs in patients on APP could be explained by the fact that FGAs are affordable and easily available in Asian countries. The association between APP and FGAs could be also due to the attempt to optimize the dopamine-2 receptor occupancy and to target a variety of receptors beyond the dopamine-2 receptor, although this practice lacks strong evidence. Frequency of APP varied considerably across Asian countries, probably owing to differences in local prescribing and psychopharmacological traditions.

The strengths of this study include its large sample size, the number of participating sites involved, and the standardized assessment. Yet, there are a few limitations that restrict the generalizability of the results. First, the study targeted only inpatients with no major medical conditions in selected Asian countries in this huge continent with a wide variety of socio-cultural, economic, and mental health care. Second, some important variables likely to influence APP prescription, such as local prescription guidelines, type of psychiatric facilities, and health insurance policies in participating study centers, were not evaluated owing to logistic reasons. Third, the data were collected by a chart review in 2001 and by either a review of case chart or patient interviews in 2004 and 2009, which might have led to observational bias. Fourth, owing to the cross-sectional design, the causality between the use of APP and demographic and clinical factors, and comparing the efficacy and safety between APP and AMP, could not be explored. Fifth, there are differences in health care schemes, prescribing traditions, treatment guidelines, and characteristics between institutions even within one country, such as China and India. The confounding effects of these differences could not be explored in this study. In addition, the cross-sectional design might lead to overestimated frequency of APP because of the cross-tapering of different antipsychotic medications that would temporarily increase APP. Finally, in this pharmacoepidemiological study with 3 separate independent samples, a small proportion of patients might be repeatedly assessed, although the wide time span between the 3 surveys minimized this possibility.

In conclusion, the results suggest that the prescription of APP for older schizophrenic inpatients in Asia is very common. Continuing education and training addressing the unnecessary use of APP and its potentially hazardous adverse effects is clearly necessary. Controlled trials exploring the efficacy, safety, and tolerability of APP are needed to inform treatment guidelines to advise physicians about the judicious use of APP in this population.

ACKNOWLEDGMENTS

The authors are grateful to the following clinicians involved in the data collection: Hong Deng and Wei Hao in China; Ajit Avasthi, Dipesh Bhagabati, Roy Abraham Kallivayalil, Shubhangi R. Parkar, and YC Jarandhar Reddy in India; Tateno Masaru, Masamune Tayoi, Akiyama Tsuyoshi, Sato Soichiro, Nakagome Kazuaki, NakamuraJun, and Kuroki Toshihide in Japan; Tae-Yeon Hwang, Seok Hyeon Kim, Yo Wang Lee, and Jong-Il Lee in Korea; Tung-ping Su, Shih-ku Lin, Zu-ting Chen, Chieh-Hsin Chang, Hong-chieh Hsu, Chi-Fa Hung, and Cheng-chun Chen in Taiwan; Krisakorn Sukavativibul, Jittima Klevelandnont, Tantawan Suradechasakul, Manote Lotrakul, Usaree Srisutadsanavong in Thailand; and Norhatringle Bahar in Malaysia. The authors also thank the clinicians who helped to organize the study in each study site.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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