Adjunctive Mood Stabilizer and Benzodiazepine Use in Older Asian Patients with Schizophrenia, 2001–2009

Abstract

Objective: This study surveyed the use of adjunctive mood stabilizers (MS) and benzodiazepines (BZD) in older Asian schizophrenia patients and examined their demographic and clinical correlates.

Method: Information on hospitalized schizophrenia patients aged 55 years or more were extracted from the database of the Research on Asian Psychotropic Prescription Patterns (REAP) study. A total of 1452 patients from 9 Asian countries and territories was included in the study. The patients’ sociodemographic and clinical characteristics and the prescriptions of antipsychotics, MS and BZD were recorded using a standardized protocol and data collection procedure.

Results: The frequency of MS prescription was 26.7% in the pooled sample, with 25.5% in 2001, 26.9% in 2004 and 27.7% in 2009. The corresponding figures for BZD were 20.7%, 20.2%, 18.4% and 23.1%, respectively. Multiple logistic regression analysis of the whole sample revealed that patients on MS were younger and more likely to be men and to have extrapyramidal side effects (EPS) and a longer duration of illness. Compared to patients in China, those in Japan were more likely to receive MS, while Korean patients were prescribed less MS. In contrast, there were no significant sociodemographic or clinical correlates of BZD use. Compared to patients in China, their Korean and Singaporean counterparts were more likely to be on BZD.

Conclusions: The use of MS and BZD is not uncommon in older Asian patients with schizophrenia. Given the paucity of empirical data on the efficacy of these agents in individuals with schizophrenia of any age and concerns about added side effects in older patients in particular, the rationale for the prescription of these agents in this population warrants further examination.

Introduction

Mood stabilizers (MS) used as adjunctive medications to antipsychotic treatment in schizophrenia are a common strategy. The rationale behind this practice is the assumption that MS could effectively control mood symptoms, such as aggression and irritability, and augment antipsychotics [1], particularly for patients who do not, or only partially, respond to antipsychotic monotherapy [2]. Yet, there is no compelling evidence to support this pharmacological strategy [3,4]. Joint use of antipsychotics and MS would increase the cost of treatment, and could lead to additional side effects and adverse drug interactions and could reduce treatment adherence [2]. Benzodiazepines (BZD) are another type of commonly used adjunctive drugs in schizophrenia administered primarily for anxiety, insomnia and in rapid tranquilization to control psychotic symptoms and agitation [5–7]. Although recommended along with antipsychotics for the treatment of acute agitation [3], continuous use of BZD for patients with schizophrenia remains controversial due to the lack of empirical research on their long-term use and their side effects including dependence, excessive sedation and cognitive dysfunction [8] that may be particularly problematic for older patients.

Over the past decades a number of studies examined the use of MS and BZD in schizophrenia. However, little is known about their use in older patients with schizophrenia although many schizophrenia patients live into older adulthood and receive treatment in their old age [9].

Regular surveys on prescription patterns in psychiatry are an efficient way of documenting the use and trend of specific treatments over time in a given clinical setting [10,11]. In order to examine the use and trend of psychotropic drug...
prescriptions in Asia, a large-scale longitudinal, observational, pharmaco-epidemiological project entitled the Research on Asian Psychotropic Prescription Patterns (REAP) was initiated in 1999 initially involving China, Hong Kong, Japan, Korea, Singapore, and Taiwan. REAP investigated the psychotropic drug prescriptions for schizophrenia inpatients in Asia. To follow the trend of pharmacotherapy in schizophrenia over the past decade, the survey was repeated in 2004 and 2009 with the same research design and protocol [7, 12]. This study is a secondary analysis of the REAP data that sought to examine (i) the frequency of MS and BZD prescriptions in older Asian patients with schizophrenia at 3 time points between 2001 and 2009 and (ii) to determine their demographic and clinical correlates.

Patients and Methods

Settings, study design, and subjects

The first survey of the REAP project was carried out in July 2001 followed by the second and third surveys in July 2004 and October 2008–March 2009, respectively, using the same design and standardized protocol. In the third round of the REAP survey the participating institutions started data collection at different times therefore the whole survey lasted 6 months but the survey at each site was completed within 1 month, consistent with the 2001 and 2004 surveys. Centers in India, Malaysia, and Thailand joined the surveys in 2009. In total, 31 psychiatric hospitals or units were involved in 2001, 25 in 2004, and 50 in 2009. Consensus meetings on data collection and uniformity of data entry were held prior to each survey. Details of the REAP project have been described elsewhere [12]. Patients involved in this study met the following criteria: (i) ICD-10 or DSM-IV schizophrenia; (ii) age of 55 years or older; and (iii) taking psychotropic drugs. Patients having clinically significant medical illnesses were excluded. Doses of antipsychotics were converted into chlorpromazine equivalent milligrams (CPZeq) [13–15]. The study was approved by the Clinical Research Ethics Committees of the respective centers. Given the anonymous nature of this observational study and the minimal risk to patients, informed consent was exempted in some study sites in line with the requirements of the local Clinical Research Ethics Committee [16] provided that only the case notes were reviewed. All patients who received the clinical interviews gave written or verbal consent according to the requirements of the respective Clinical Research Ethics of the Clinical Committees, which varied across different study sites during the study period.

Eligible patients were enrolled consecutively at each site during the study period and the data collection was completed within 1 month. Patients’ sociodemographic and clinical characteristics including age, sex, length of illness, the presence or absence of significant psychiatric symptoms within the past month, extrapyramidal side effects (EPS) and tardive dyskinesia (TD), type and doses of antipsychotic medications and MS and BZD [as required prescriptions (p.r.n.)] of BZD within the past 24 h were also counted] prescribed were collected by reviewing case notes in 2001, and by either a review of case notes only or a review of case notes supplemented by a clinical interview in both 2004 and 2009 using a questionnaire designed for the study. The data were collected by the attending psychiatrists of the patients or by members of the research team with the agreement of the psychiatrist in charge of the patient. In REAP surveys, psychotropic drugs were categorized according to the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) system [17, 18], and MS include valproate, lithium, carbamazepine, phenobarbital, phenytoin, lamotrigine, topiramate and zonisamide.

Results

A total of 1,452 patients met the above criteria and formed the study sample; 388 (26.7 %) received MS in the pooled sample; 125 (25.5 %) in 2001, 120 (26.9 %) in 2004, and 143 (27.7 %) in 2008. The corresponding figures for BZD were 300 (20.7 %), 99 (20.2 %), 82 (18.4 %) and 119 (23.1 %), respectively. Table 1 presents the sociodemographic and clinical features of the study population. The most commonly used MSs were valproate, carbamazepine and lithium, while most commonly used BZDs were lorazepam, clonazepam and diazepam. Fig. 1 shows the prescription of MS and BZD by study sites. MS was most frequently administered in Japan and China while Malaysia and India had the highest rates of use of BZD. Table 2 shows the independent socio-demographic and clinical correlates of MS and BZD prescriptions. Multivariate analyses revealed that patients on MS were younger and more likely to be men and had EPS, and longer duration of illness. Compared to patients in China, those in Japan were more likely to receive MS, while Korean patients were less likely to be prescribed these agents. In contrast, no independent socio-demographic or clinical correlates of BZD use were found. However, compared to patients in China, Korean and Singaporean patients were more likely to take BZD.

Discussion

To the best of our knowledge, this was the first international study examining the prescription of MS and BZD for older schizophrenia patients. Given that older schizophrenia patients usually have multiple somatic problems, difficulties with cognition and vision, reduced drug clearance and narrow therapeutic window [19, 20], it was expected that frequencies of MS and BZD would be lower than the figures in younger schizophrenia patients. This was not supported by the findings; 26.7 % and 20.7 % of participants received MS and BZD, respectively, in higher frequencies than their younger counterparts reported in a considerable proportion of literature. In an Australian cohort of schizophrenia patients (age range: 18–64 years) 10.6 % received MS (Castle et al. [21]). In a survey covering 10 European countries 7–19 % of schizophrenia patients (≥18 years) were on MS [22]. In Hong Kong 10.2 % and 25.1 % of schizophrenia patients (age: 42.3 ± 8.9 years) received MS and BZD, respectively; the corresponding figures in mainland China (age: 43.7 ± 7.9 years) were 3.2 % and 34.8 % [5, 23].
Table 1  Sociodemographic and clinical characteristics of older Asian patients with schizophrenia in REAP surveys (2001–2009)*.

<table>
<thead>
<tr>
<th></th>
<th>China (n = 215)</th>
<th>Hong Kong (n = 43)</th>
<th>India (n = 5)</th>
<th>Japan (n = 826)</th>
<th>Korea (n = 128)</th>
<th>Singapore (n = 84)</th>
<th>Taiwan (n = 143)</th>
<th>Malaysia (n = 8)</th>
<th>Total (n = 1452)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (years)</td>
<td>59.5 (5.3)</td>
<td>62.7 (6.4)</td>
<td>57.0 (2.1)</td>
<td>64.2 (6.8)</td>
<td>59.8 (4.5)</td>
<td>60.6 (4.8)</td>
<td>60.1 (5.4)</td>
<td>58.8 (3.5)</td>
<td>62.4 (6.5)</td>
</tr>
<tr>
<td>CPZeq (mg/d)</td>
<td>431 (334)</td>
<td>404 (379)</td>
<td>508 (163)</td>
<td>636 (616)</td>
<td>577 (528)</td>
<td>429 (410)</td>
<td>394 (311)</td>
<td>331 (175)</td>
<td>556 (539)</td>
</tr>
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<table>
<thead>
<tr>
<th>Length of illness</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>&lt;5 (years)</td>
<td>19 (8.8)</td>
<td>3 (7.0)</td>
<td>1 (20.0)</td>
<td>16 (1.9)</td>
<td>5 (3.9)</td>
<td>6 (7.1)</td>
<td>3 (2.1)</td>
<td>1 (12.5)</td>
<td>54 (3.7)</td>
</tr>
<tr>
<td>men</td>
<td>114 (53.0)</td>
<td>23 (53.5)</td>
<td>5 (60.0)</td>
<td>436 (52.8)</td>
<td>54 (42.2)</td>
<td>45 (53.6)</td>
<td>81 (56.6)</td>
<td>4 (50.0)</td>
<td>760 (52.3)</td>
</tr>
<tr>
<td>positive symptoms</td>
<td>116 (54.0)</td>
<td>25 (58.1)</td>
<td>5 (100)</td>
<td>562 (68.0)</td>
<td>90 (70.3)</td>
<td>39 (46.4)</td>
<td>93 (65.0)</td>
<td>5 (62.5)</td>
<td>935 (64.4)</td>
</tr>
<tr>
<td>negative symptoms</td>
<td>151 (70.2)</td>
<td>28 (65.1)</td>
<td>4 (80.0)</td>
<td>597 (72.3)</td>
<td>64 (50.0)</td>
<td>34 (40.5)</td>
<td>86 (60.1)</td>
<td>1 (12.5)</td>
<td>965 (66.5)</td>
</tr>
<tr>
<td>EPS</td>
<td>32 (14.9)</td>
<td>24 (55.8)</td>
<td>6 (120)</td>
<td>270 (32.7)</td>
<td>38 (29.7)</td>
<td>8 (9.5)</td>
<td>56 (39.2)</td>
<td>4 (50.0)</td>
<td>433 (29.8)</td>
</tr>
<tr>
<td>TD</td>
<td>13 (6.0)</td>
<td>11 (25.6)</td>
<td>0 (0)</td>
<td>74 (9.0)</td>
<td>6 (4.7)</td>
<td>3 (3.6)</td>
<td>23 (16.1)</td>
<td>2 (25.0)</td>
<td>132 (9.1)</td>
</tr>
<tr>
<td>FGA1</td>
<td>82 (38.1)</td>
<td>19 (44.2)</td>
<td>2 (40.0)</td>
<td>588 (71.2)</td>
<td>89 (69.5)</td>
<td>12 (85.7)</td>
<td>56 (39.2)</td>
<td>6 (75.0)</td>
<td>914 (62.9)</td>
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<tr>
<td>SGA2</td>
<td>161 (74.9)</td>
<td>22 (51.2)</td>
<td>4 (80.0)</td>
<td>513 (62.1)</td>
<td>61 (47.7)</td>
<td>7 (8.3)</td>
<td>97 (67.8)</td>
<td>2 (25.0)</td>
<td>867 (59.7)</td>
</tr>
<tr>
<td>MS</td>
<td>54 (25.1)</td>
<td>8 (18.6)</td>
<td>0 (0)</td>
<td>259 (31.4)</td>
<td>14 (10.9)</td>
<td>19 (22.6)</td>
<td>34 (23.8)</td>
<td>0 (0)</td>
<td>388 (26.7)</td>
</tr>
</tbody>
</table>

| Frequently used MS |                  |                    |               |                |                |                    |                |                |                 |
| valproate         | 7 (3.3)           | 5 (11.6)           | 0 (0)         | 83 (10.0)      | 7 (5.5)        | 13 (15.5)          | 10 (7.0)       | 0 (0)          | 125 (8.6)       |
| carbamazepine     | 0 (0)             | 1 (2.3)            | 0 (0)         | 68 (8.2)       | 3 (2.3)        | 5 (6.0)            | 2 (1.4)        | 0 (0)          | 79 (5.4)        |
| lithium           | 5 (2.3)           | 1 (2.3)            | 0 (0)         | 60 (7.3)       | 1 (0.8)        | 2 (2.4)            | 0 (0)          | 0 (0)          | 69 (4.8)        |
| BZD              | 33 (15.3)         | 10 (23.3)          | 2 (40.0)      | 139 (16.8)     | 46 (35.9)      | 32 (38.1)          | 33 (23.1)      | 5 (62.5)       | 300 (20.7)      |

| Frequently used BZD |                  |                    |               |                |                |                    |                |                |                 |
| lorazepam         | 9 (4.2)           | 6 (14.0)           | 2 (40.0)      | 39 (4.7)       | 31 (24.2)      | 4 (4.8)            | 27 (18.9)      | 5 (62.5)       | 123 (8.5)       |
| clonazepam        | 47 (21.9)         | 5 (11.6)           | 0 (0)         | 37 (4.5)       | 4 (3.1)        | 3 (0.0)            | 24 (16.8)      | 0 (0)          | 117 (8.1)       |
| diazepam          | 2 (0.9)           | 3 (7.0)            | 0 (0)         | 23 (2.8)       | 14 (10.9)      | 27 (32.1)          | 1 (0.7)        | 0 (0)          | 70 (4.8)        |

CPZeq = chlorpromazine equivalents; EPS = extrapyramidal symptoms; TD = tardive dyskinesia; FGA = first-generation antipsychotic; SGA = second-generation antipsychotic; MS = mood stabilizer; BZD = benzodiazepine
* % = percentage of all patients; there was no older patients in Thailand
1 Any use of FGA
2 Any use of SGA
The common use of MS and BZD could be due to the following reasons. REAP surveys targeted only in-patients who were more likely to present with severe illness, more symptoms of violence and of mood disturbance, or had a history of mood symptoms. Concerns about withdrawal effects and deterioration of mental state following the cessation of MS and BZD may prevent psychiatrists from discontinuing these drugs. A sizeable minority of Asian patients and their families are unwilling to give up the earlier prescribed drugs due to fear of relapse even if their therapeutic effects are not satisfactory [10]. Another historical reason is the traditional medical concept in Asia that favors the combination of drugs with different pharmacological properties as more effective despite the lack of compelling evidence for this practice [24]. In this context it should be noted that neither MS nor BZD has been approved by the US Food and Drug Administration for the treatment of schizophrenia [25]. Considering that older patients usually have multiple medical problems, often take a variety of drugs and are more sensitive to adverse effects of pharmacotherapy compared to younger patients [26], co-administration of antipsychotics with MS or BZD in older schizophrenia patients requires extra caution and close monitoring.

Multivariate analysis revealed that patients on MS were younger and were more likely to be men and had EPS and longer duration of illness. Similar to earlier findings [4, 23, 27], more male than female patients received MS in this study, which could be due to the fact that male patients often present with more aggressive...
and impulsive behaviors [28]. Patients on MS experienced more severe EPS in this study, providing some support for the notion that a combination of antipsychotics, particularly FGAs and MS could increase the risk of EPS [29]. Longer duration of illness was also associated with more frequent use of MS. This association could be possibly explained by refractory symptoms often displayed by hospitalized patients with a longer length of illness. Risks of adverse drug effects of psychotropic drugs increase with age [26] and younger patients are usually more aggressive and show mood fluctuations, which could possibly explain the association between relatively younger age in this group and more frequent prescription use of MS in this study. No associations were found between BZD and any demographic or clinical variables in this study. Yet, the possibility that BZD use might correlate with some unmeasured variables, such as anxiety and sleep problems cannot be excluded.

Prescription patterns of MS and BZD varied considerably across Asian countries, probably owing to the variability of local precribing and psychopharmacological traditions, economic factors, health insurance and mental health policies in the participating countries.

The results of this study should be interpreted with caution because of several methodological limitations. First, the REAP project surveyed only inpatients in selected Asian countries and territories using a non-random sampling method, and patients in participating countries or territories were not nationally representative, hence the findings are not applicable to all older Asian patients with schizophrenia. Second, the cross-sectional design of the study did not allow the determination of causal relationships between MS and BZD prescriptions and other variables. Third, in this pharmaco-epidemiological study with 3 separate samples, a small proportion of patients might be repeatedly assessed, although the wide time span between the 3 surveys minimized this possibility. Fourth, there were few older patients with schizophrenia in some participating countries and territories, which hinders the analyses of MS and BZD use in each site by diagnostic category. Fifth, due to the lack of standardized diagnostic tools, in this study, the possibility that some patients with schizoaffective or bipolar disorders with psychotic symptoms were misdiagnosed as schizophrenia could not be excluded, resulting in increased use of MS. Finally, the severity of psychopathology and drug-induced side effects were only assessed by dichotomous variables rather than standardized instruments.

In conclusion, prescriptions of MS and BZD were not uncommon for older Asian patients with schizophrenia. Considering the increased risk of drug-induced side effects in this patient population, an examination of the rationale of their use is clearly warranted. Specific guidelines for the treatment of Asian older schizophrenia patients with adjunctive pharmacotherapies should be developed.

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Conflict of Interest

The authors declare no conflicts of interest.

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