Common use of anticholinergic medications in older patients with schizophrenia: findings of the Research on Asian Psychotropic Prescription Pattern (REAP) study, 2001–2009


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Objective: This study surveyed the use of anticholinergic medications (ACMs) in older Asian patients with schizophrenia and examined its demographic and clinical correlates.

Method: A total of 1452 hospitalized patients with schizophrenia aged 55 years or older in nine Asian countries and territories were surveyed between 2001 and 2009. The cross-sectional data of patients’ socio-demographic and clinical characteristics and the prescriptions of antipsychotic drugs and ACM were recorded using a standardized protocol and data collection procedure.

Results: The frequency of ACM prescription was 64.6% in the pooled sample, with 72.4%, 61.9%, and 59.5% in 2001, 2004, and 2009, respectively. Multiple logistic regression analysis of the whole sample revealed that patients on ACM who had a higher dose of antipsychotic medications were more likely to have extrapyramidal side effects and to receive first-generation antipsychotic medications.

Conclusions: Anticholinergic medications were frequently used in older Asian patients with schizophrenia. Considering the potential side effects of ACM, the rationale for their widespread use in this patient population should be revisited. Copyright © 2012 John Wiley & Sons, Ltd.

Key words: schizophrenia; prescription patterns; anticholinergic; older patients; Asia

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Introduction

Extrapyramidal side effects (EPS), induced by postsynaptic dopaminergic (D2) blockade of antipsychotics, are one of the most common causes for non-adherence to treatment leading to preventable morbidity, mortality, and economic costs for schizophrenia (Knapp, 1997; Lindstrom & Bingefors, 2000). Anticholinergic medications (ACMs) are often used to treat EPS as they can improve treatment adherence (Goff et al., 1991; Lavin and Rifkin, 1991) and have minimal euphoriant effects at therapeutic doses (Vagen and Gotestam, 1986). However, they can cause a number of central (such as impaired concentration, confusion, attention deficit, and memory impairment) and peripheral anticholinergic side effects (such as dry mouth, constipation, urinary retention, bowel obstruction, dilated pupils, blurred vision, increased heart rate, and decreased sweating). These side effects can be debilitating and more problematic for older patients or patients with preexisting conditions than for other individuals with schizophrenia (Brebin et al., 2004; Lieberman, 2004; Minzenberg et al., 2004). In addition, ACM can also worsen positive psychotic symptoms (Tandon and Greden, 1989) and elevate risk for tardive dyskinesias (TD; Perris et al., 1979). The necessity and duration of their prescription have been controversial issues (Ungvari et al., 1999; Carnahan et al., 2006). In the past decade, use of ACM has been surveyed in patients with schizophrenia (Ascher-Svanum et al., 2004; Xiang et al., 2007). To date, there are limited data about the use of ACM in older patients with schizophrenia, although many such patients live into older adulthood (Kohen et al., 2010).

In order to maximize the benefits and reduce the inappropriate use of psychotropic medications in Asian psychiatric patients, in 1999, a large-scale longitudinal, observational pharmacoepidemiological project entitled the Research on Asian Psychotropic Prescription Pattern (REAP) study was initiated in six Asian countries and territories comprising China, Hong Kong, Japan, Korea, Singapore, and Taiwan. The REAP studies investigated prescription trends for psychotropic medications in hospitalized patients with schizophrenia in Asia. To follow the trend in prescription patterns for schizophrenia over the past decade, the prescription of psychotropic medications in the participating Asian countries and territories was surveyed again in 2004 and 2009 using the same study design.

This study is a secondary analysis of the data of the REAP project that set out (1) to determine the ACM prescription in older Asian patients with schizophrenia during the period between 2001 and 2009 and (2) to explore its demographic and clinical correlates. Given the heightened vulnerability to drug-induced side effects and poorer general health status of older patients (Uchida et al., 2009; Meyers and Jeste, 2010) and the widespread use of second-generation antipsychotics (SGAs) that are less likely to induce EPS (Leucht et al., 2003), we hypothesized that only a small proportion of older patients with schizophrenia would receive ACM in REAP surveys.

Methods

Settings, study design, and subjects

The first survey of the REAP project was conducted in July 2001 followed by investigations in July 2004 and October 2008–March 2009 using the same design and standardized protocol. India, Malaysia, and Thailand joined the surveys in 2009. Thirty-one psychiatric facilities were involved in 2001, 25 in 2004, and 50 in 2009. Details of the REAP project have been described elsewhere (Chong et al., 2004; Tor et al., 2011). Participating patients satisfied the following study criteria: (1) ICD-10 or DSM-IV 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 (CPZeq; APA, 1997; Kane et al., 1998; Woods, 2003).

Eligible patients were recruited consecutively, and their socio-demographic and clinical characteristics including age, gender, length of illness, type and doses of antipsychotic medications and ACM prescribed, the presence or absence of significant psychiatric symptoms within the past month, and EPS were collected by a review of case notes only or a review of case notes supplemented by a clinical interview in 2004 and 2009 using a questionnaire designed for the study in all three occasions. These data were collected by the patients’ attending psychiatrists or by members of the research team with the agreement of the psychiatrist in charge of the patient. In REAP surveys, psychotropic drugs are categorized according to the World Health Organization Anatomic Therapeutic Chemical (WHO-ATC) system (WHO Collaborating Centre for Drug Statistic Methodology, 2002; Chong et al., 2010). ACMs include trihexyphenidyl, biperiden, benztpoline, promethazine, procyclidine, amantadine, piroheptine, and mazaticol.

The study was approved by the Clinical Research Ethics Committees 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 (Shinfuku and Tan, 2008) 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.

Statistical analysis

The data were analyzed using SPSS 13.0 for Windows. ACM prescriptions were compared between the three surveys by chi-squared test and antipsychotic doses in CPZeqmg between patients with and without ACM by Mann–Whitney U test. Multiple logistic regression analysis with the “Enter” method was used to determine the demographic and clinical variables influencing prescription of ACM. Use of ACM was the dependent variable, whereas independent variables included age, gender, psychopathology, length of illness, dose of antipsychotics, use of first-generation antipsychotics (FGAs), presence of EPS and TD, and study sites and time. The level of significance was set at 0.05 (two-tailed).

Results

Altogether 1490 patients fulfilled the study criteria from the REAP database. Of them, 938 (64.6%) patients received ACM in the three REAP surveys with 355 (72.4%) in 2001, 276 (61.9%) in 2004, and 307 (59.5%) in 2009. Results of a univariate analysis indicate that there was a significant difference among the three surveys in the use of ACM (χ² = 18.0, d.f. = 2, p < 0.001). Table 1 presents the socio-demographic and clinical characteristics of the whole sample and separately by study site. Of patients on FGAs (n = 914), 705 (77.1%) received ACM, whereas 506 (58.4%) of those on SGAs (n = 87) received ACM. Dose of antipsychotics in CPZeq was 627 ± 581 and 425 ± 422 mg in patients on ACM and those not, respectively, and there was a significant difference (z = −8.0, p < 0.001) between the two groups by Mann–Whitney U test.

Discussion

The main finding of this study is that in aggregate 63.4% of older Asian patients with schizophrenia were prescribed ACM, with only a slight decrease over the decade (72.4%–61.9%–59.5%). These results do not support the hypothesis that only a small proportion of this patient population would receive ACM. The most commonly used ACMs were biperiden and trihexyphenidyl. The results of ACM use in this study were basically consistent with previous findings in Asian adult patients with schizophrenia; for example, 62% of adult inpatients with schizophrenia aged 40.0 ± 14.3 years in Hong Kong received ACM (Ungvari et al., 2002); the corresponding figure in a random sample of 505 Chinese outpatients with schizophrenia aged 18–60 years was 47.7% (Xiang et al., 2007).

The frequent use of ACM in this sample could be possibly due to the following reasons: (1) a considerable proportion of patients was experiencing EPS, likely from high doses of FGAs; (2) concerns about rebound effects and deterioration in mental state following the cessation of ACM (Gray and Gournay, 2000); (3) Asian patients and/or their families are frequently unwilling to give up earlier prescribed drugs either not trusting the psychiatrist or fear of relapse (Ungvari et al., 1997); and (4) the prevailing general principle of traditional medicine in Asia that a combination of multiple drugs with different pharmacological components is more effective although there is no unequivocal evidence for this practice (Binder et al., 1987). Considering the generally poor health status and increased vulnerability to psychotic side effects among older patients with schizophrenia (Feng et al., 2008; Uchida et al., 2009), ACM should be prescribed with caution for this group. Frequency and type of ACM varied considerably across Asian countries, probably due to differences in local prescribing and psychopharmacological traditions, health policy, and insurance.

Anticholinergic medication is primarily used for the treatment and prophylaxis of EPS (Xiang et al., 2007). As expected, more patients with EPS and those on FGA were on ACM in this study whereas the
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<th>Japan (n = 828)</th>
<th>57.0 6.8</th>
<th>636 616</th>
<th>77 528</th>
<th>409 110</th>
<th>394 311</th>
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<tr>
<td>Positive symptoms</td>
<td>542 68.0</td>
<td>52 42.2</td>
<td>45 53.6</td>
<td>81 56.6</td>
<td>4 50.0</td>
<td>760 52.3</td>
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<tr>
<td>Negative symptoms</td>
<td>562 68.0</td>
<td>54 52.8</td>
<td>54 42.2</td>
<td>81 56.6</td>
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<tr>
<td>EPS</td>
<td>56 56.6</td>
<td>64 50.0</td>
<td>40 16.0</td>
<td>86 60.1</td>
<td>1 12.5</td>
<td>965 66.5</td>
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<td>TD</td>
<td>80 65.0</td>
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<td>FGA a</td>
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<tr>
<td>ACM</td>
<td>56 56.6</td>
<td>64 50.0</td>
<td>40 16.0</td>
<td>86 60.1</td>
<td>1 12.5</td>
<td>965 66.5</td>
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There were no older patients in Thailand.

aAny use of FGA.
bAny use of SGA.

CPZeq = chlorpromazine equivalents; FGA = first-generation antipsychotic; SGA = second-generation antipsychotic; ACM = anticholinergic medications; EPS = extrapyramidal symptoms; TD = tardive dyskinesia.
association of ACM with antipsychotic doses (OR 1.0004, 95% CI 1.0–1.001) was statistically, but not clinically, significant. Because of co-linearity between use of FGAs and SGAs, we only entered FGAs in the multivariate analysis. In order to explore the association between SGAs and use of ACM, the multiple logistic regression was repeated with SGAs as one of the potential correlates. Less patients on SGAs than those not on these drugs received ACM (p < 0.001, OR 0.5, 95% CI 0.4–0.6), which could be related to fact that SGAs are less likely to induce EPS (Leucht et al., 2003).

The strengths of this study are the large sample size, the inclusion of several Asian countries and territories, and the standardized procedure of data collection. However, the results should be interpreted with caution because of several methodological limitations. First, the REAP project focuses on inpatients in nine selected Asian countries and territories; hence, the findings cannot be applied to all patients with schizophrenia in Asia. Second, the severity of psychopathology and the EPS was assessed by dichotomous variables, rather than standardized instruments. Third, the causality between use of ACM and demographic and clinical variables could not be identified because of the cross-sectional study design. Fourth, there were few older patients with schizophrenia in some participating countries and territories, which hinders the analyses of ACM prescription in each site by different study time. Fifth, a host of important variables likely to influence ACM prescription, such as the length of antipsychotic treatment and that of the schizophrenic illness, separate examination of early-onset and late-onset schizophrenia, local prescription guidelines, smoking, the type of psychiatric facilities, and mental health policies, was not evaluated. In addition, there are differences in health care schemes, prescribing traditions and treatment guidelines between institutions even within one country, and within one institution between different study times. The confounding effects of these differences could not be explored. Finally, the appropriateness and duration of ACM prescription were not surveyed. There is no well-established equivalent dose conversion for ACMs; therefore, the total dose of ACM prescribed and its demographic and clinical correlates could not be examined.

In conclusion, the results suggest that ACM is frequently used in older inpatients with schizophrenia in Asia. An examination of the appropriateness and reasons for prescribing ACM, and the extent to which these older patients are experiencing ACM-induced adverse effects is warranted. In addition, a careful risk–benefit analysis of their use in individual patients is also needed.

To date, there have been no specific guidelines for the use of ACM in older patients with schizophrenia, but the following principles may be considered: ACM could be used (1) in the acute treatment of schizophrenia or if EPS has occurred (Ungvari et al.
Conflict of interest

No conflict of interest declared.

Key points

- No large scale international studies have reported on the prescribing patterns of anticholinergic medications in older Asian patients with schizophrenia.
- The results indicate that the prescription of ACM for older schizophrenia inpatients in Asia is very common.
- Considering the potentially deleterious side effects of ACM, the rationale for their widespread use in this patient population should be revisited.

Acknowledgements

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Anticholinergic medications in treatment of schizophrenia


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