Use of Anticholinergic Drugs in Patients with Schizophrenia in Asia from 2001 to 2009

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Abstract

Objective: The aim of this study was to survey the use of anticholinergic medication (ACM) in Asia between 2001 and 2009 and examine its demographic and clinical correlates.

Method: A total of 6761 hospitalized schizophrenia patients in 9 Asian countries and territories were examined between 2001 and 2009. The patients' socio-demographic and clinical characteristics and the prescriptions of psychotropic drugs were recorded using a standardized protocol and data collection procedure.

Results: The frequency of ACM prescription decreased from 66.3% in 2001, to 52.8% in 2004 and 54.6% in 2009, with wide inter-country variations at each time period. Multiple logistic regression analysis of the whole sample showed that patients taking ACM presented with more severe positive, negative, and extrapyramidal symptoms. They were also more likely to receive first-generation and depot antipsychotics and antipsychotic polypharmacy, and less likely to receive second-generation ones.

Conclusions: The wide variation in ACM prescription across Asia suggests that a combination of clinical, social, economic and cultural factors play a role in determining the use of these drugs. Regular reviews of ACM use are desirable to reveal the discrepancy between treatment guidelines and clinical practice.

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Introduction

The use of anticholinergic drugs (ACM) in the treatment of drug-induced extrapyramidal side effects (EPS) has been a controversial issue, particularly their continuous prescription in chronic schizophrenia [1–3]. Side effects related to ACM are cognitive impairment [4,5], the potential for abuse [6], central anticholinergic syndrome at higher doses [7], worsening of positive symptoms [8], and elevated risk for tardive dyskinesia (TD) [9]. Nevertheless, ACM can improve patients' treatment adherence [2,10] and have no euphoriant effects at therapeutic doses [11].

Preliminary evidence suggests that Asian patients require lower doses of antipsychotics and that they are more sensitive to EPS compared with their Western counterparts [12,13]. Repeated surveys in the same region are more useful than a single survey because longitudinal studies can reveal important trends in pharmacotherapy over time and help to evaluate the effectiveness of education and training of clinicians. Sim et al. [14] found that 34.7–82% of 2399 schizophrenia inpatients in 6 Asian countries and territories in 2001 were taking ACM. Since the 2001 survey, economic factors, health-care policies, and health insurance in Asia have changed considerably, accompanied by the widespread use of second-generation antipsychotic drugs (SGAs) and intensive continuing medical education programs organized by professional associations and drug companies. To determine the current trend in prescribing patterns of ACM in this region, the survey was repeated in 2004 and 2009 with the same design and instruments.

This study set out (i) to examine the prescription pattern of ACM and its trend over time in schizophrenia inpatients in Asia; and (ii) to explore the demographic and clinical correlates of ACM use in the pooled sample with an increase in power compared with the baseline survey conducted in 2001 [14].

Patients and Methods

Settings, study design, and subjects

The study was part of the Research on Asian Psychotropic Prescription Pattern (REAP) project,

which is an ongoing pharmaco-epidemiological survey designed to reflect the prescription trends of psychotropic drugs in hospitalized schizophrenia patients in 6 Asian countries and territories, including mainland China (in the following: China), Hong Kong, Taiwan, Singapore, Japan, and Korea using a standardized protocol and data collection procedure. Centers in India, Malaysia, and Thailand joined the survey in 2009. The 3 REAP surveys were conducted in July 2001, July 2004, and October 2008 – March 2009. Details of the REAP project methodology have been described elsewhere [15,16]. Participating patients needed to satisfy the following study criteria: (i) ICD-10 or DSM-IV schizophrenia; (ii) be able to comprehend the aims of the study; and (iii) be willing to provide written or oral consent according to the requirements of the clinical research ethics committees in the respective study sites. Patients suffering from major medical conditions were excluded. The study was approved by the Institutional Review Boards of the respective centers.

Eligible patients were recruited consecutively, and their socio-demographic and clinical variables including age, sex, the type and dose of antipsychotics, significant symptoms (both positive and negative) within the past month, and extrapyramidal side effects, tardive dyskinesia (TD), and use of antipsychotic medications at the study time were collected by a review of medical records in 2001, and by either a review of medical records or patient interview in both 2004 and 2009 using a questionnaire designed for the study. Only a review of medical records was used in some participating centers due to logistic reasons. The data were collected by the attending psychiatrist of the patient at the time of study or by members of the research team (experienced psychiatrists) with the agreement of the psychiatrist in charge of the patient. Doses of antipsychotic drugs were converted into chlorpromazine equivalent milligrams (CPZeq) [17–19]. TD is treated separately from other forms of EPS because of its special characteristics and treatment strategy compared with other extrapyramidal symptoms. Consensus meetings on data collection and the uniformity of data entry were held before each survey. In REAP surveys, psychotropic drugs were categorized according to the World Health Organization Anatomic Therapeutic Chemical (WHO-ATC) system [20,21], and ACMs include trihexyphenidyl, biperiden, benztropine, promethazine, procyclidine, amantadine, piroheptine and mazaticol.

Statistical analysis

The data were analyzed using SPSS 13.0 for Windows. Comparisons among the 3 cohorts with respect to the proportion of individuals prescribed ACM in each study site were conducted using chi-square (χ^2) tests. The comparisons between ACM and non-ACM groups with respect to socio-demographic and clinical characteristics were performed by independent samples t-test, Mann-Whitney U-test, and chi-square test, as appropriate. Multiple logistic regression analysis was used to determine the independent contribution of demographic and clinical variables to ACM use. The level of significance was set at 0.05 (2-tailed).

Results

Altogether, 6761 patients were involved in the investigations; 2399, 2136, and 2226 patients in 2001, 2004, and 2009, respect ively. **Table 1** displays the socio-demographic and clinical characteristics of the whole sample and separately by study site and time. There was a significant decrease in the frequency of

Table 1 Socio-demographic and clinical characteristics and anticholinergic drug prescription in 2001, 2004, and 2009.

	China			Hong Kong			Japan			Korea			Singapore			Taiwan			India	Thailand	Malaysia	Total		
	2001	2004	2009	2001	2004	2009	2001	2004	2009	2001	2004	2009	2001	2004	2009	2001	2004	2009	2009	2009	2009	2001	2004	2009
patients (n)	611	504	409	108	100	100	627	583	514	442	412	284	300	91	100	311	446	499	181	39	100	2399	2136	2226
age (yrs)																								
mean	38.5	38.9	42.5	45.4	39.9	40.9	52.9	52.2	51.5	39.1	41.0	43.5	46.3	40.7	42.8	38.2	39.2	44.2	32.1	37.7	37.2	43.6	43.1	43.9
SD (CPZeq mg/d)	12.9	14.6	13.1	13.5	11.1	13.4	13.5	15.0	15.4	9.5	10.9	11.8	10.8	9.9	10.4	10.8	10.8	10.8	10.8	10.2	10.7	13.5	14.2	13.7
mean	447	463	546	557	490	525	906	676	637	687	652	725	604	534	397	489	494	496	483	630	374	641	568	559
SD	323	308	370	663	298	347	843	670	510	559	557	566	517	452	323	388	337	362	499	328	274	611	499	447
men (%)	50.9	51.8	69.7	58.3	51.0	47.0	58.4	57.6	55.6	57.0	59.7	55.6	58.7	53.8	50.0	55.6	62.8	68.9	46.4	69.2	72.0	55.9	57.3	60.6
positive symptoms (%)	60.9	65.3	52.1	68.5	84.0	63.0	63.2	71.5	80.7	71.3	77.2	79.9	47.0	84.6	80.0	73.3	67.7	76.8	93.4	94.9	75.0	63.6	71.5	74.7
negative symptoms (%)	49.1	72.4	70.7	71.3	75.0	9.0	74.3	66.2	59.3	45.0	36.4	45.8	29.3	37.4	9.0	41.2	50.4	47.1	47.0	12.8	8.0	52.4	57.8	48.3
EPS (%)	18.8	11.5	20.0	71.3	73.0	19.0	28.7	32.9	24.3	37.1	27.2	23.9	12.3	27.5	13.0	39.5	30.9	41.1	30.4	7.7	28.0	29.0	28.0	26.9
TD (%)	3.1	1.4	2.7	22.2	20.0	2.0	6.7	7.7	4.9	3.8	4.4	2.1	2.7	4.4	2.0	1.3	10.3	6.2	2.2	0	4.0	4.8	6.6	3.8
FGA (%)	47.3	35.1	24.2	49.1	26.0	24.0	87.4	66.6	52.9	72.9	66.3	46.1	84.3	81.3	49.0	52.1	38.3	37.7	30.9	82.1	78.0	67.8	51.9	41.7
SGA (%)	64.0	75.6	83.9	46.3	68.0	50.0	50.4	75.6	85.0	37.1	45.9	75.0	6.7	16.5	50.0	48.6	64.6	73.5	80.7	30.8	23.0	45.5	64.7	73.7
ACM (%)	34.7	44.4	36.4	50.0	46.0	40.0	87.1	70.2	64.4	76.0	33.5	68.0	82.0	73.6	67.0	63.3	54.7	53.3	56.9	74.4	37.0	66.3	52.8	54.6

Centers in India, Malaysia and Thailand joined the survey in 2009; EPS = extrapyramidal side effects; TD = tardive dyskinesia; CPZeq = chlorpromazine equivalents; FGA = first-generation antipsychotics; SGA = second-generation antipsychotics; ACM = anticholinergic drugs

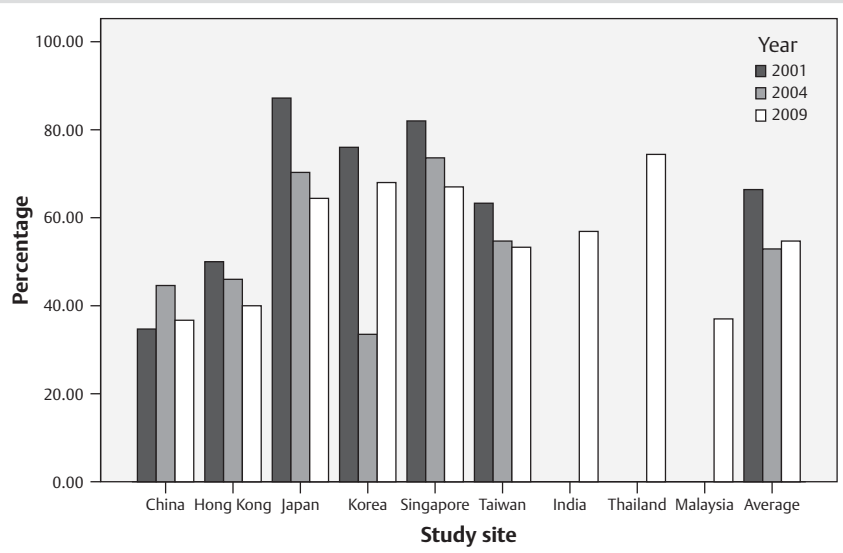

Fig. 1 Use of ACM in 2001, 2004 and 2009.

	Non-ACM group (n = 2827)		ACM group (n = 3934)		Statistics		
	Mean	SD	Mean	SD	z	df	P-value
age (year)	42.1	13.9	44.6	13.6	−7.2[a]	–	<0.001
antipsychotic dose (CPZeq mg/d)	501	419	656	585	−10.3[a]	–	<0.001
	N	*%*	*N*	*%*	χ^2	*df*	*P-value*
men	1595	56.4	2319	58.9	4.3	1	0.04
positive symptoms	1892	66.9	2823	71.8	18.2	1	<0.001
negative symptoms	1462	51.7	2106	53.5	2.2	1	0.1
EPS	586	20.7	1306	33.2	126.9	1	<0.001
tardive dyskinesia	144	5.1	195	5.0	0.1	1	0.8
depot antipsychotic	191	6.8	682	17.3	162.6	1	<0.001
APP	778	27.5	2128	54.1	473.9	1	<0.001
FGA	985	34.8	2680	68.1	734.0	1	<0.001
SGA	2059	72.8	2056	52.3	292.3	1	<0.001

Table 2 Comparison of the ACM and non-ACM groups with regard to socio-demographic and clinical characteristics in the whole sample (n = 6761).

[a] Mann-Whitney U-test

EPS = extrapyramidal side effects; CPZeq = chlorpromazine equivalents; APP = antipsychotic polypharmacy; FGA = first-generation antipsychotics; SGA = second-generation antipsychotics; ACM = anticholinergic drugs

ACM use in the whole sample, from 66.3% in 2001 to 52.8% in 2004, and to 54.6% in 2009 ($\chi^2 = 102.5$, df = 2, $p < 0.001$). As for the study sites, the decrease was significant in Japan ($\chi^2 = 85.9$, df = 2, $p < 0.001$), Singapore ($\chi^2 = 10.6$, df = 2, $p = 0.005$), and Taiwan ($\chi^2 = 8.5$, df = 2, $p = 0.01$), while the frequency of ACM use increased in China ($\chi^2 = 12.0$, df = 2, $p = 0.002$). In Hong Kong the frequency of ACM use decreased over time, but this was not significant ($\chi^2 = 2.1$, df = 2, $p = 0.3$). Korea had a significant change between the 3 surveys ($\chi^2 = 172.6$, df = 2, $p < 0.001$), with a decrease in 2004, and then an increase in 2009. **Fig. 1** presents use of ACM in participating countries and regions over the study period.

Table 2 compares the socio-demographic and clinical characteristics of the ACM and non-ACM groups for the whole sample. **Table 3** shows the independent factors that were significantly associated with ACM use. Patients taking ACM presented with more severe positive, negative symptoms and EPS. They were also more likely to receive first-generation (FGAs) and depot antipsychotics and antipsychotic polypharmacy, and less likely to receive SGAs.

Discussion

The results show that ACM use significantly decreased in Asia between 2001 and 2009, but these drugs were still extensively prescribed for more than half of the patients in this region. This is basically in keeping with the findings of previous studies of Asian schizophrenia inpatients. Chong et al. [22] found that 64% of schizophrenia patients in long-stay wards in Singapore received ACM. Wu et al. [23] reported that 58.2% of schizophrenia inpatients were on ACM in a major psychiatric hospital in China, while in Hong Kong the figures were 67.8% and 61.8% in 1996 and 1999, respectively. There could be several explanations for the high proportion of ACM prescriptions in this study. Asian patients have a lower threshold for the therapeutic and side effects of drugs compared with Caucasians [13,24], although this notion has been questioned [25], leading to more ACM use for prophylaxis and treatment. Another factor could be the widely held belief in Asian societies that a combination of multiple drugs with different pharmacological features is more effective [26]. Some clinicians are also concerned about the rebound phenomena and the subsequent deterioration in patients' mental state following the cessation of ACM [27,28].

Table 3 Factors associated with prescription of ACM in the whole sample by multiple logistic regression analysis with the non-ACM group as reference (n = 6 441).

	P-value	Odds ratio	95% C.I.
age (year)	0.2	1.0	0.99 – 1.001
antipsychotic dose (CPZeq mg/d)	0.06	1.0	1.0 – 1.0
men	0.9	1.01	0.9 – 1.1
positive symptoms	< 0.001	1.3	1.2 – 1.5
negative symptoms	0.006	1.2	1.1 – 1.3
EPS	< 0.001	1.9	1.7 – 2.2
tardive dyskinesia	0.052	0.8	0.6 – 1.003
depot antipsychotic	< 0.001	2.3	1.8 – 3.0
APP	< 0.001	1.4	1.2 – 1.7
FGA	< 0.001	2.4	1.9 – 2.8
SGA	0.001	0.7	0.6 – 0.9
study sites			
– China	–	1.0	–
– Hong Kong	0.5	0.9	0.7 – 1.2
– Japan	< 0.001	3.3	2.8 – 3.9
– Korea	< 0.001	1.7	1.4 – 2.0
– Singapore	< 0.001	1.9	1.4 – 2.6
– Taiwan	< 0.001	1.9	1.6 – 2.3
study time			
– 2001 survey	–	1.0	–
– 2004 survey	< 0.001	0.6	0.6 – 0.7
– 2009 survey	0.004	0.8	0.7 – 0.9

Centers in India, Malaysia and Thailand joined the survey in 2009, therefore they were not included in multiple logistic regression analysis

EPS = extrapyramidal side effects; TD = tardive dyskinesia; CPZeq = chlorpromazine equivalents; APP = antipsychotic polypharmacy; FGA = first-generation antipsychotics; SGA = second-generation antipsychotics; ACM = anticholinergic drugs

The decrease in ACM use over time in the whole sample as well as in Japan, Singapore and Taiwan probably reflects the increased use of SGAs in this region and reduced doses of antipsychotics, which reduces the likelihood of EPS. Another reason may be that efforts to educate clinicians and inform their practices in recent years have effectively narrowed the gap between clinical practice and treatment guidelines. Treatment guidelines do not recommend the prophylactic use of ACM; it should be used only when Parkinsonian symptoms have developed and the reduction of antipsychotic doses or the use of another antipsychotic drug causing fewer Parkinsonian side effects has proved ineffective. ACM should, and can [3,29], be gradually withdrawn if Parkinsonian symptoms remit [30–33]. It should be noted that ACM use increased significantly in China from 2001 to 2004, although the frequencies of ACM use were still relatively low compared with most other sites in each of the 3 surveys. The prescription pattern of ACM in Korea was unusual in that it decreased by 2004 and then again increased by 2009. We assume that this pattern could be due to the increased dose of antipsychotics in 2009 (725 mg CPZeq) compared to 2001 (687 mg CPZeq) and 2004 (652 mg CPZeq) necessitating the prophylactic use of ACM.

There was considerable variation in ACM use across the study sites, ranging from 34.7% (China) to 82% (Singapore) in 2001, 33.5% (Korea) to 73.6% (Singapore) in 2004, and 36.7% (China) to 68.0% (Korea) in 2009. This suggests that a host of local prescribing and psychopharmacological traditions, socio-cultural factors, health-care policy, health insurance, and biological differences within the study population could all play a role in determining the prescription of ACM.

Patients on ACM were very similar to patients without ACM in terms of age and dose of antipsychotics. Patients with severe positive and negative symptoms were more likely to be prescribed ACM. This association was expected because more severe symptoms usually necessitate higher antipsychotic doses and antipsychotic polypharmacy [34,35], and consequently an elevated risk of EPS. Prophylactic use of ACM is also more often considered in these severely ill patients.

ACM are primarily prescribed for the prophylaxis and treatment of EPS. It was therefore expected that more patients with EPS would be on ACM. It has been documented that the continuous use of ACM may contribute to the development of TD [9,36], which explains why patients with TD were less likely to be prescribed ACM although the trend did not reach a significant level (p = 0.052). Prescribing a combination of FGAs and ACM is common practice [23,37–39], as was found in this study. As all depot antipsychotics in the REAP surveys were first-generation drugs, patients on depot were more likely to have ACM. SGAs are less likely to induce EPS [40], which explains their negative association with ACM in this study. The more frequent prescriptions of ACM to patients receiving antipsychotic polypharmacy (APP) could be accounted for by the attempt to prevent the anticipated EPS related to APP [1].

The strengths of this study are its large sample size and the number of participating study centers involved. The main limitations include the following. First, the generalizability of the results is limited because the study targeted only inpatients. Second, the severity of psychopathology and drug-induced side effects were not quantitatively assessed. Third, the conversion of different antipsychotics into CPZeq is only a rough estimation, particularly for SGAs [38]. Finally, some important factors likely to influence ACM prescription, such as local prescription guidelines, type of psychiatric facilities (such as chronic *vs*. acute psychiatric hospitals) and reimbursement policies were not evaluated.

In conclusion, the results suggest that the prescription of ACM for schizophrenia inpatients in Asia has gradually decreased over recent years, but these drugs are still being prescribed for more than half of the inpatients with schizophrenia. Considering the increased use of SGAs and the fact that continuous administration of ACM often gives rise to distressing and disabling side effects, prescription of ACM should be further reduced. It is important to emphasize the need to regularly monitor ACM prescriptions with particular attention to their unnecessary use for long-term prevention of EPS.

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