

Trends in the access to and the use of antipsychotic medications and psychotropic co-treatments in Asian patients with schizophrenia

Y.-T. Xiang^{1*}, G. S. Ungvari², C. U. Correll³, H. F. K. Chiu⁴ and N. Shinfuku⁵

¹ Unit of Psychiatry, Faculty of Health Sciences, University of Macau, Macao SAR, China

² School of Psychiatry & Clinical Neurosciences, University of Western Australia, Perth, Australia

³ Division of Psychiatry Research, The Zucker Hillside Hospital, North Shore-Long Island Jewish Health System, Glen Oaks, NY, USA

⁴ Department of Psychiatry, Chinese University of Hong Kong, Hong Kong SAR, China

⁵ International Centre for Medical Research, Kobe University School of Medicine, Kobe, Japan

To date, antipsychotics remain the mainstay of treatment for schizophrenia and related disorders although other psychotropic medications and non-pharmaceutical interventions have been used adjunctively in some patients and settings. Regular surveys on access to and prescription patterns of psychotropic medications in clinical practice are an important and efficient way of examining the use and time trends of treatments in a given population and region. Unlike developed Western countries, Asian countries have not fully undergone deinstitutionalisation of the severely and chronically mentally ill, and community-based mental health services are still under-developed. As a result, a large number of psychiatric patients still receive treatments in psychiatric hospitals. Moreover, there have been very limited studies examining access to and prescription patterns of psychotropic medications for schizophrenia patients in Asian countries. In this paper, we focus on the only international project on the use of psychotropic medications in schizophrenia patients in selected East and Southeast Asian countries/territories summarising its major findings. Most of the first- and second-generation antipsychotics (FGAs and SGAs) are available in Asian countries, but the access to psychotropic medications is largely affected by socio-cultural and historical contexts, health insurance schemes, health care policy, medication cost and consumers' preference across different countries/territories. Overall, the proportional use of FGAs, high dose antipsychotic treatment and antipsychotic polypharmacy have decreased, while the use of SGAs and antidepressants have increased and the utilisation of benzodiazepines and mood stabilisers has remained relatively stable over time. However, within these general trends, there is great inter-country variation regarding the psychotropic prescribing patterns and trends in Asian schizophrenia patients that also seems to differ from data in many Western countries.

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Introduction

Nowadays most treatment guidelines on the use of psychotropic drugs are based on randomised controlled trials. However, significant differences exist between the patients studied in pre-marketing clinical trials and those treated in real-world clinical practice (Martin *et al.* 2004). In order to improve inter-individual homogeneity, in pre-marketing trials, small samples of patients are usually selected from target populations with stringent study criteria. Generally, psychiatric and relevant medical comorbidities as well as co-medications are excluded, and the focus is on high internal validity, paying the price of reduced

generalisability or 'external validity' (Correll *et al.* 2011). In contrast, in clinical practice, psychiatrists often use medications and medication combinations in ways that have not been studied in either pre- or post-marketing trials. For example, they may prescribe the medication at different doses or to different groups of patients than studied but who have the same disease, may use different treatment combinations, or even target different indications (off-label use).

Antipsychotic medications have been introduced in Asia since the 1950s and soon became the mainstay of treatment for schizophrenia and related disorders. In the past decades, developing community-based mental health services have been encouraged in many Asian societies, but due to many historical, economic and socio-cultural reasons, a large number of psychiatric patients still receive hospital-based services. As a result, the numbers of psychiatric beds in many

* Address correspondence: Dr Y.-T. Xiang, Faculty of Health Sciences, University of Macau, Avenida da Universidade, 3/F, Building E12, Taipa, Macau SAR, China.
(E-mail: xyutly@gmail.com)

Asian countries have not decreased, or have even been increasing (Shinfuku & Tan, 2008).

Psychotropic medication utilisation varies greatly across different countries and over time (Rothbard *et al.* 2003; Bowers *et al.* 2004). This has to do with different thresholds for illness identification and pharmacologic intervention, availability and acceptability of alternative treatment approaches, levels of stigma and help-seeking, barriers to and availability of care. Thus, it is not surprising that psychotropic medication utilisation also varies greatly in Asia. For example, in Japan high dose antipsychotic use and antipsychotic polypharmacy were common, Singapore had high utilisation of antipsychotic depot injections and in China clozapine was used extensively (Chong *et al.* 2004). However, cautious interpretation of the observational results is necessary, as medication utilisation primarily depends on the availability of the medication, drug regulatory and health delivery systems, medication cost and coverage and marketing by pharmaceutical companies. In order to rationalise their use, it is important to understand access to, trends and patterns of psychotropic medication use in clinical practice.

Access to and prescription patterns of psychotropic medications have been extensively examined in North America and European countries (Bowers *et al.* 2004; Huskamp, 2005; Gallego *et al.* 2012a). In contrast, very limited studies have been performed in Asian countries. To the best of our knowledge, to date only one international, pharmaco-epidemiological project has been conducted in Asia. For the purpose of this paper, we introduce the methodology of this international, pharmaco-epidemiological study and summarise its major findings, which will help put into perspective data from other regions in the world.

The research on Asian psychotropic prescription pattern (REAP) project

In 1999 an international collaborative research group comprising psychiatrists, pharmacologists and epidemiologists initiated a large-scale longitudinal, observational, pharmaco-epidemiological project entitled the Research on East Asia Psychotropic Prescriptions (REAP) study. The REAP project examined the prescription trends for psychotropic drugs in schizophrenia inpatients in six Asian countries and territories (China, Hong Kong, Japan, Korea, Singapore and Taiwan). The first REAP survey was carried out in July 2001 (REAP-AP1) followed by the second and third surveys in July 2004 (REAP-AP2) and October 2008–March 2009 (REAP-AP3), respectively, using the same design and standardised protocol. India, Malaysia and Thailand joined the REAP project in

REAP-AP3 therefore the project was renamed as Research on Asian Psychotropic Prescription Pattern (REAP).

Prior to each survey, consensus meetings were held to agree upon the procedures of data collection and data entry. The original English version of the data collection forms was translated into the local languages of the participating countries and territories. Patients were diagnosed with schizophrenia according to either DSM-IV or ICD-10 criteria. Psychotropic medications were classified according to the Anatomical Therapeutic Chemical classification by the WHO Collaborating Centre for Drug Statistics Methodology (WHO Collaborating Centre for Drug Statistic Methodology, 2002).

Demographic and clinical characteristics including use of antipsychotics, benzodiazepines antidepressants and mood stabilisers were collected using a data collection form designed for the study. The data were collected based on a review of medical records in 2001 and by either a review of medical records alone or a review supplemented by a clinical interview in 2004 and 2009 in different study sites. Data were collected by the patients' treating psychiatrists or by members of the research team with the agreement of the psychiatrist in-charge of the patient. Each national/territorial coordinating centre was responsible to establish the dataset with a uniform data entry sheet, which were sent to the overall coordinators in Taipei, Taiwan and Kobe, Japan for compilation and statistical analyses.

Mental health resources in Asian countries and territories

Table 1 shows mental health resources in the countries and territories participating in the REAP study. Of the Asian countries/territories, Japan had the largest number of psychiatric beds and psychiatrists per capita, followed by Korea. In contrast, India and Thailand had the lowest number of psychiatric beds and psychiatrists per capita. Altogether, 31 psychiatric facilities participated in 2001, 25 in 2004 and 50 in 2009 in REAP surveys.

Access to psychotropic medications

Table 2 following the first antipsychotic medication, chlorpromazine, other first-generation antipsychotics (FGAs) were introduced into Asia between the 1960s and 1980s. second-generation antipsychotics (SGAs) were introduced into Asia since the 1990s, except for clozapine, which was introduced to Asia in the 1970s.

Clozapine was developed by the pharmaceutical company Wander Laboratories in 1959; however, it

Table 1. Mental health resources in participating countries and territories (World Health Organisation, 2011)

	Population (1000)	Psychiatrists per 100 000	Psychiatric beds per 10 000	Total psychiatric beds
China	1 354 146	1.5	1.5	199 318
India	1 214 464	0.3	0.2	27 835
Japan	126 995	10.1	27.7	352 437
Thailand	68 139	0.4	1.3	8774
Korea	48 500	5.1	19.0	92 382
Malaysia	27 913	0.8	1.8	5106
Taiwan*	22 879	3.7	7.5	1716
Hong Kong	7069	4.4	5.1	3589
Singapore	4836	2.8	4.2	2044

*Taiwan was not included in the WHO ATLAS-2011, therefore we listed the data in the WHO ATLAS-2005 (Shinfuku & Tan, 2008).

was removed from the market in the USA and some European countries later in the 1970s because it can induce potentially fatal agranulocytosis in rare cases (Idanpaan-Heikkila *et al.* 1975). Due to its unique efficacy in treating refractory schizophrenia (Kane *et al.* 1988) and the introduction of regular monitoring of white blood cell count to reduce the risk of agranulocytosis, the US Food and Drug Administration (FDA) approved clozapine again in the early 1990s, but restricted its use to patients with treatment resistant to schizophrenia. In contrast, in China clozapine has been widely used even as a first-line treatment since its introduction in 1976 (Liu & Li, 2003; Xiang *et al.* 2007b). In Japan, however, clozapine had not been approved until the end of 2009.

Nowadays, most of FGAs and SGAs are available in Asian countries/territories involved in the REAP surveys. However, patient access and prescribing habits of clinicians in each Asian country are multi-determined. Individual factors include country-level insurance coverage, cost, ease and speed of generics penetrating the market, physician-level incentives if they also function as pharmacists. Some examples in specific countries are detailed in an exemplary fashion below.

The reimbursement and specific license of medications approved by governments plays the decisive role in the availability of psychotropics. For example, there were only four SGAs available in Japan and seven in Taiwan in 2004 when the second REAP survey was carried out (Shinfuku & Tan, 2008). Some of these differences have to do with whether the local body approving new medications evaluates data collected in different populations and submitted to the USA or European licensing bodies, or whether studies in samples from the specific Asian country are required to concern about significant genetic differences that may translate in clinically relevant

pharmaco-kinetic and/or pharmaco-dynamic differences. One example is Japan, when, as mentioned before, clozapine was approved as late as 2009 and where greater restrictions to the use of clozapine exist, such as initiation only during inpatient stay.

In China, clozapine is one of the cheapest antipsychotics, costing only US\$ 0.08 for 300 mg. In addition, clozapine and risperidone were the only SGAs covered by public health insurance before 2005. Consequently, clozapine was the most widely used SGA in practice. In addition, competition between imported and locally manufactured products greatly influences the access to psychotropic medications. Locally manufactured, generic psychotropic medications, particularly novel antipsychotics and antidepressants, are usually approved by China FDA and then are introduced into market after or, even before, the patent protection period of their imported counterparts expires. The efficacy and adverse events of locally manufactured psychotropic medications are mostly sufficiently similar to the patented products (Yin *et al.* 2005; Li *et al.* 2006), but their price is merely around one third or half of the branded counterparts. Therefore, locally produced generics are more likely preferred by some patients, their families and sometimes even treating psychiatrists, which determines the availability of imported SGAs and antidepressants in many hospitals.

In Japan, all patients receiving psychiatric care are covered by national insurance system. Treatment costs are compensated equally for private and public psychiatric hospitals. In principle, patients need to pay 10% or 30% of their treatment costs and the rest is compensated by public funds. However, long stay in private and public psychiatric hospitals could be subsidised by the life protection scheme; therefore patient's payments are exempted. This medical compensation system might have contributed to the high dose prescription and polypharmacy in Japan.

Table 2. Socio-demographic and clinical characteristics and psychotropic drug prescription in Asia in 2001, 2004, and 2009

Survey time	China			Hong Kong			Japan			Korea			Singapore			Taiwan			India	Thailand	Malaysia	Total			
	01*	04*	09*	01*	04*	09*	01*	04*	09*	01*	04*	09*	01*	04*	09*	01*	04*	09*	09*	09*	09*	01*	04*	09*	
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	
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	
CPZeq (mg/d; %)																									
<300	34.9	35.7	25.2	29.6	28.0	27.0	16.9	23.8	24.7	21.0	22.1	13.7	33.7	40.7	51.0	33.1	30.9	33.1	29.3	12.8	43.0	27.0	28.7	27.5	
300–999	57.6	56.5	63.1	53.7	68.0	61.0	51.2	57.1	56.8	54.8	58.7	60.9	49.0	46.2	42.0	56.9	58.7	56.5	67.4	71.8	52.0	54.1	57.7	58.8	
≥1000	7.5	7.7	11.7	16.7	4.0	12.0	31.9	19.0	18.5	24.2	19.2	25.4	17.3	13.2	7.0	10.0	10.3	10.4	3.3	15.4	5.0	18.9	13.6	13.6	
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	
APP (%)	25.2	23.8	35.9	35.2	24.0	23.0	78.6	67.1	60.9	35.5	37.6	44.4	70.3	75.8	74.0	22.2	13.2	26.9	45.9	64.1	41.0	46.8	38.3	43.4	
BZD	7.2	24.8	16.6	23.1	40.0	26.0	22.5	25.4	21.8	49.3	25.5	50.0	51.3	80.2	47.0	27.7	25.3	27.7	37.6	7.7	52.0	27.8	28.3	29.5	
MS	24.9	23.2	30.6	31.5	40.0	32.0	35.6	36.7	37.0	25.6	21.8	38.7	31.0	27.5	28.0	37.3	33.4	36.1	10.5	35.9	16.0	30.5	29.7	32.1	
AD	4.7	5.8	8.1	0.9	14.0	8.0	2.2	2.2	2.7	3.4	1.9	10.9	15.3	15.4	22.0	7.4	13.7	13.2	5.0	7.7	7.0	5.3	6.5	8.7	

AD, antidepressant; APP, antipsychotic polypharmacy (more than 1 antipsychotic medication); BZD, benzodiazepine; CPZeq, chlorpromazine equivalents; EPS, extrapyramidal symptoms; FGA, first-generation antipsychotic; MS, mood stabiliser; SGA, second-generation antipsychotic.

Mood stabilisers include valproate, lithium, carbamazepine, phenobarbital, phenytoin, lamotrigine, topiramate and zonisamide.

Centres in India, Malaysia and Thailand joined the survey in 2009.

*01 = 2001, 04 = 2004, 09 = 2009.

In Singapore, on the other hand, the more common use of depot antipsychotics in public psychiatric hospitals is encouraged due to treatment cost containment and less artificial separation between the medication budget and the budget paying for expensive hospitalisations. Conversely, the very low use of depot antipsychotics in China that has been reported to be 2.8% only (Si, 2014), is due to the fact that depot medications, especially SGA injectables are not yet covered by the government and will need to be paid by patients and families.

Prescription trends of FGAs and SGAs

SGAs have significant advantages over FGAs in reducing all-cause discontinuation, improving (or less worsening of) negative symptoms and global cognition and causing less extrapyramidal symptoms, although they may increase the risk of metabolic syndrome (Zhang *et al.* 2013). However, we found in the REAP surveys that although the prescribing rates of FGAs decreased over time (67.8% in 2001, 51.9% in 2004 and 41.7% in 2009), there were still approximately half of patients in the participating Asian countries receiving FGAs in the whole sample. The underlying reasons behind this unexpected finding cannot be examined with confidence based on the current cross-sectional design. Nevertheless, we speculate that socio-economic and cultural factors including psychopharmacological traditions, prior antipsychotic treatment, uneven access to different antipsychotics, higher cost of SGAs and insurance and health policy restrictions may determine the ongoing frequent use of FGAs in Asian schizophrenia patients (Xiang *et al.* 2012b). However, a recent network meta-analysis of 212 acute phase studies of antipsychotics in patients with schizophrenia (Leucht *et al.* 2013) showed that individual antipsychotics differed substantially in efficacy and side-effects, challenging the crude classification of antipsychotics into FGAs and SGAs, which are both heterogeneous. Therefore the choice of antipsychotics should depend on the needs of individual patients and take prior therapeutic and adverse effect patterns, access and affordability all into account. Table 3 shows the most commonly prescribed antipsychotic drugs.

Use of high dose antipsychotics

The use of high antipsychotic doses has been controversial in clinical practice. Most treatment recommendations do not recommend high antipsychotic doses (Buchanan *et al.* 2010; Kreyenbuhl *et al.* 2010). Studies failed to find convincing evidence for improved

Table 3. The most commonly prescribed antipsychotic drugs and antidepressants in Asia in 2001, 2004 and 2009

	2001		2004		2009	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
FGAs						
Haloperidol	690	28.8	387	18.1	412	18.5
Chlorpromazine	561	23.4	349	16.3	251	11.3
Sulpiride	232	9.7	178	8.3	129	5.8
Fluphenzine decanoate	112	4.7	38	1.8	66	3.0
Flupentixol decanoate	95	4.0	52	2.4	85	3.8
SGAs						
Risperidone	472	19.7	631	29.5	689	31.0
Clozapine	348	14.5	340	15.9	331	14.9
Olanzapine	114	4.8	226	10.6	352	15.8
Quetiapine	86	3.6	167	7.8	226	10.2
Aripiprazole	0	0	0	0	113	5.1
Antidepressants						
Fluoxetine	28	1.2	27	1.3	27	1.2
Fluvoxamine	14	0.6	17	0.8	40	1.8
Trazodone	12	0.5	38	1.8	34	1.5
Paroxetine	8	0.3	17	0.8	11	0.5
Sertraline	5	0.2	9	0.4	30	1.3

%, percentage of all patients; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

efficacy with high antipsychotic doses, but the risk of extrapyramidal side effects (Pierre, 2005) and hyperprolactinemia (Byerly *et al.* 2007) was dose-related. The percentage of high dose antipsychotics of 15.5% across the three REAP survey time points (2001: 18.9%, 2004: 13.6%, 2009: 13.6%) depends on treatment settings and populations, but is in the lower range compared with Western findings of 15.4–41% (Webb & Agnew, 1975; Buchanan *et al.* 2010; Kreyenbuhl *et al.* 2010). The percentage of high antipsychotic doses was particularly prominent in Japan. Based on the current study design we cannot identify the reasons for the common use of high antipsychotic doses in Japan, except for assuming that probably clinical traditions might play an important role. In addition, it was reported that sometimes sedation was the primary purpose of pharmacotherapy for schizophrenia inpatients in Japan (Fujii & Shinfuku, 2005; Shinfuku & Tan, 2008), which may partly also explain the common use of high antipsychotic doses.

Use of high antipsychotic doses significantly decreased over time in Asian patients, which is mainly driven by changes in Japan. It was reported that the presentations at academic meetings and relevant publications about the findings based on REAP surveys may have enhanced Japanese clinicians' awareness of rational prescription practices (Shinfuku & Tan, 2008).

Antipsychotic polypharmacy

Although two meta-analyses suggested that antipsychotic polypharmacy may have superior efficacy compared with antipsychotic monopharmacy (Barbui *et al.* 2009; Correll *et al.* 2009), results were inconclusive. The reason that antipsychotic polypharmacy could not be recommended was that in both meta-analyses, data were relatively scarce, a publication bias could not be excluded and certain moderators of the efficacy lowered the level of the evidence. While, antipsychotic polypharmacy is associated with the potential for increased hospitalisation rates, increased side effects and higher treatment cost and increased mortality (Elie *et al.* 2010; Tiihonen *et al.* 2012; Gallego *et al.* 2012b). Based on these findings, several attempts have been made to reduce antipsychotic polypharmacy in clinical practice settings (Essock *et al.* 2011; Tani *et al.* 2013).

The frequency of antipsychotic polypharmacy of 43% found in the whole REAP sample across the three surveys is higher than the frequencies found pooled analysis from 147 studies across four decades, finding pooled antipsychotic polypharmacy frequencies of 16% in North America and 23% in Europe (Gallego *et al.* 2012a). However, the REAP project showed a slight decrease in the use of antipsychotic polypharmacy in schizophrenia inpatients in Asia from 46.8% in 2001 to 38.3% in 2004, and 43.4% in 2009 (Xiang *et al.* 2012c).

Adjunctive antidepressant prescriptions

Depressive symptoms are common in schizophrenia leading to potentially serious consequences (Conley, 2009). Therefore, antidepressants are not infrequently co-prescribed with antipsychotics, although the rationale for this strategy is still controversial (Himelhoch *et al.* 2012). In the REAP surveys only a small proportion of patients (6.8% in the pooled sample) received antidepressant treatment with increasing frequency from 5.3% in 2001 to 6.5% in 2004, and to 8.7% in 2009. This slight increase might possibly be explained by the introduction and widespread use of novel antidepressants that are generally better tolerated than tricyclic antidepressants.

The frequency of antidepressant prescriptions in Asian schizophrenia patients is significantly lower than the figures in Western patients. The Clinical Trials of Intervention Effectiveness study in the USA found that 38% of patients received at least one antidepressant (Chakos *et al.* 2006). Himelhoch *et al.* (Himelhoch *et al.* 2012) reported that 37.4% of outpatient veterans with schizophrenia received an antidepressant prescription in the USA. One possible

reason for this difference in antidepressant prescribing for patients with schizophrenia may be a different level of awareness of comorbid depression in schizophrenia between Asian and Western settings (Xiang *et al.* 2013). Another reason for this difference may lie in the fact that the utility of antidepressants for negative symptoms, demonstrated in several meta-analyses (Rummel *et al.* 2006; Sepehry *et al.* 2007; Singh *et al.* 2010; Hecht & Landy, 2012), may either be interpreted differently, or that negative symptoms are considered less as a viable treatment target in Asia. Finally, the low rate of antidepressant use in Asian patients may be due to the lack of compelling evidence for the usefulness of antidepressant use in schizophrenia in general (Himelhoch *et al.* 2012). Table 3 presents the most commonly prescribed antidepressants.

Adjunctive mood stabiliser and benzodiazepine prescriptions

Mood stabilisers and benzodiazepines are commonly used as adjunctive medications with antipsychotic treatment in schizophrenia. The rationale behind this practice is that mood stabilisers may help control aggression and irritability and augment antipsychotics (Citrome, 1995) for patients who do not, or only partially respond to antipsychotic monotherapy (Parepally *et al.* 2002). Benzodiazepines are prescribed primarily for anxiety, insomnia and as part of rapid tranquillisation aiming to control psychotic symptoms and agitation (Xiang *et al.* 2007a; Tor *et al.* 2011). However, there is lack of compelling evidence to support these adjunctive medications (Citrome *et al.* 2000; Chen *et al.* 2007; Buchanan *et al.* 2010). Conversely, concurrent use of antipsychotics, mood stabilisers and benzodiazepines may increase the risk of additional side effects, the cost of treatment and reduce treatment adherence (Parepally *et al.* 2002).

In the whole sample of the three REAP surveys, 30.8 and 28.5% of patients received mood stabilisers and benzodiazepines, respectively. These rates were higher than reported in the literature. For example, in Australia 10.6% of schizophrenia patients received mood stabilisers (Castle *et al.* 2002). In a study covering ten European countries, 7–19% of schizophrenia patients received mood stabilisers (Haro & Salvador-Carulla, 2006). The common use of mood stabilisers and benzodiazepines in Asian countries may be due to the following reasons. REAP surveys involved only hospitalised patients who were more likely to suffer from more mood disturbance and symptoms of violence or agitation. Further, concerns about withdrawal effects and deterioration of the mental state following the cessation of mood stabilisers and benzodiazepines may prevent psychiatrists from discontinuing these

drugs (Ungvari *et al.* 1997; Xiang *et al.* 2012a). Moreover, in Asia there is a traditional medical belief that the combination of medications with different pharmacological properties is more effective despite the lack of compelling evidence for this practice (Binder *et al.* 1987). In this context, it should be noted that neither mood stabilisers nor benzodiazepines have been approved by the US FDA for the treatment of schizophrenia (Pickar *et al.* 2008).

Concluding comments

The comparison of the three completed REAP surveys may approximate trends in the prescription patterns of psychotropics for schizophrenia inpatients in Asia. However, because the study sample comprised only hospitalised patients in nine Asian countries and territories and in selected institutions in these countries and territories, the results cannot be generalised to all schizophrenia populations in Asia. *More Asian countries should be included in future REAP surveys or similar projects.* In addition, some important variables, such as prior psychotropic treatment, treatment targets and duration and treatment response and adverse effects, were not recorded in the REAP surveys. Finally, the REAP surveys did not cover West Asia.

Nevertheless, the results of the REAP survey indicate that access to and prescription patterns of psychotropic medications for patients with schizophrenia in Asia differ considerably across countries and territories and over time, and are still considerably different from those reported in Western settings. The rationale and appropriateness of these prescription patterns need to be examined further. In future surveys in Asia and elsewhere, it should be attempted to add data that capture the rationale for and outcome of certain treatment practices, include data on adherence patterns and patient-centred outcomes, such as treatment satisfaction and quality of life, and/or link survey data to registries that capture hospitalisation and mortality data at a minimum.

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Conflict of Interest

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