Research on Asian Prescription Patterns (REAP): Focusing on Data from Japan

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Since 2001, Asian psychiatrists have carried out collaborative research on the prescription patterns of psychotropic drugs in Asia (REAP). Investigators, who participated in the survey in 2001 and 2004, were from China, Hong Kong, Japan, Korea, Singapore, and Taiwan. In 2008, investigators from India, Malaysia, and Thailand also joined this research. All investigators collected the data based on a unified questionnaire-based research protocol. More than 6,000 prescriptions of schizophrenic inpatients, (around 2,000 prescriptions each in 2001, 2004, and 2008), were analyzed and compared. The results have yielded that Japan has notable high-dose antipsychotic prescription and high frequency of polypharmacy than other participating countries and areas, that the availability of particular drugs differs greatly from country to country, and that there has been a major shift in the prescriptions from first-generation antipsychotics (FGAs) to second-generation antipsychotics (SGAs) in all participated Asian countries from 2001 to 2008. This shift has been accompanied by changes in side effects and by the use of other psychotropic drugs. These findings have been reported in more than 30 international journals. In 2004, REAP members surveyed the prescription patterns of antidepressants and did a follow up survey in 2013. More than 200 psychiatrists of 40 psychiatric institutions from 10 countries and areas in Asia participated in the recently concluded 2013 survey. The goal of REAP has been to improve prescription patterns of psychotropic drugs in those participated Asian countries. REAP has potential to promote collaborative research in psychiatry among developed and developing countries in Asia.

Key words: schizophrenia, antipsychotic drugs, polypharmacy, antidepressants

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Introduction

"International Collaborative Studies on Psychotropic Prescription" is the largest and the longest international collaborative research project in Asia. The study is known by Research on Asia Psychotropic Prescription Pattern (REAP). REAP undertook a large scale survey on prescription patterns of schizophrenic inpatients in Asia

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for three times (2001, 2004 and 2008) and on the use of antidepressants twice (2004 and 2013). In 2013, psychiatrists and pharmacists from 10 countries and areas participated in the survey. The countries and areas included both developed countries (Japan, Korea, Taiwan, Hong Kong, and Singapore) and developing countries (China, Malaysia, Thailand, India, and Indonesia). Countries and areas in Asia differ greatly by the population size, the level of socio-economic development, hygienic conditions, and mental health resources.

In the past 10 years, the findings of REAP surveys were reported many times at the World Congress of the World Psychiatric Association (WPA) and other major international congress. Also, the investigators published many papers based on REAP surveys. The papers have been mostly written in English, and more than 30 papers have been accepted by well-recognized international scientific journals. The references section of this overview paper lists the papers based on REAP surveys. The author is grateful for the kind invitation by the *Taiwanese Journal of Psychiatry* to write this overview on REAP. The detailed outcomes of the surveys can be found in articles listed in the reference section of this overview. I will touch only outlines of the major findings. I will rather focus on the beginning, development, and present situation of REAP, as well as on the REAP impact on the prescription patterns of psychotropic prescription in Japan.

The History of REAP

Beginning of REAP

The beginning of REAP was dated back at the Symposium on Neuro-psychopharmacology, December 2-4, 1999 at National University of Singapore, Singapore [1]. The symposium was jointly supported by National University of Singapore (NUS) and the Japan Society for the Promotion of Sciences (JSPS). International Center for Medical Research (ICMR) of Kobe University School of Medicine represented the JSPS in medical fields.

The Department of Pharmacology of NUS proposed "New Challenges in Neuro-psychopharmacology" as the title of the symposium. More than 30 leaders in psychiatry and psychopharmacology attended the symposium from Japan, Indonesia, Malaysia the Philippines, Singapore and Thailand. The symposium coincided with the 40th anniversary of the Department of Pharmacology of NUS. Many presentations by psychiatrists and pharmacologists from Asian countries made it clear that prescriptions of psychotropic drugs differ greatly country by country. At the symposium, a collaborative research project was discussed to survey the prescriptions of schizophrenic in patients in participating countries. The purpose of the collaborative research was intended to improve the prescriptions of psychotropic medications in Asia. The unified research protocol and the questionnaire were prepared after many communications by e-mails among interested researchers from different countries.

Members had to clear several technical issues. The diagnostic tools used for the diagnoses of schizophrenia were different among participating countries. *Diagnostic and Statistical Manual (DSM)* was used in Korea and Taiwan. China used *Chinese Classification of Mental Diseases -Version 3 (CCMD-3)* which was the Chinese version of the *International Classification of Diseases (ICD)*. Both *DSM* and *ICD* were used in Japan [2]. Diagnostic criteria for schizophrenia in China with *CCMD-3* were the same as those by *ICD-10* [3]. After a series of discussion, participating psy-

chiatrists agreed to input the cases diagnosed as schizophrenia using *ICD-10*, *DSM-IV* and *CCMD-3*. REAP members had to formulate a comprehensive table to enable the chlorpromazine equivalence comparison covering all antipsychotic drugs available in Asia. Inagaki et al. had already prepared the chlorpromazine equivalence table for all antipsychotics available in Japan [4]. But the table made by Inagaki et al. has not covered several antipsychotics used in other countries participated in the survey [5].

We adopted the use of *Anatomical Chemical Classification Index with Defined Daily Doses (ATC-DDD)*, to classify all psychotropic drugs used in the survey. *ATC-DDD* was developed, and updated every year by WHO Collaborating Center for Drug Statistics Methodology in Oslo, Norway [6]. *ATC-DDD* is a classification system for all kind of drugs as *ICD* is a classification system for all kinds of diseases. It took almost one year to agree on the research protocol and the questionnaire. The thrusts of the REAP protocol were to record all the prescriptions of schizophrenic inpatients at the same day at different centers in different countries and areas in Asia. The schizophrenic inpatients had to meet the diagnostic criteria using *ICD-10*, *DSM-IV*, and *CCMD-3*.

Cases were collected from inpatient populations which research collaborators in different countries and areas had easy access as doctors in charge. This method, called as "window" or "handy sampling," is often used to collect data in countries with scarce resources. Therefore, REAP is not an epidemiological survey in strict sense but an amalgamation of surveys in different countries using the same questionnaire based on a unified research protocol. By analyzing a large sample collected from different countries and areas, it became possible to understand prescription patterns for schizophrenic inpatients in Asia. This simple research protocol and handy survey method contributed REAP to last more than 10 years in countries with limited psychiatric resources. The first prescription survey on inpatients with schizophrenia was carried out in July 2001. In February 2002, researchers from China, Hong Kong, Indonesia, Japan, Korea, Malaysia, Singapore, and Taiwan reported the outcomes of the collaborative survey at Kobe University. Data reported from a few countries were not complete with several missing inputs and had to be removed from the overall analysis.

More than 2,000 prescriptions of schizophrenic inpatients were collected from six countries and areas: China, Hong Kong, Japan, Korea, Singapore, and Taiwan. The findings from the first survey in 2001 were presented at the 12th World Congress of World Psychiatric Association (WPA) held in Yokohama in August 2002. The survey in 2001 reported the dominant use of the first-generation of antipsychotics (FGAs) such as chlorpromazine and haloperidol over the second-generation antipsychotics (SGAs). Among countries and areas participated in the survey, Japan was marked with polypharmacy and high-dose prescription of antipsychotics. In China, clozapine was the most commonly prescribed antipsychotic drug. Singapore was marked with the frequent use of depot form antipsychotics.

Patients in Hong Kong have been reported to have a high frequency of side effects. This finding has been interpreted as having high sensitivity of Hong Kong psychiatrists to watch for side effects. Overall findings of the survey of 2001 were reported both in English [7] and in Japanese [8]. Papers on polypharmacy and high-dose prescription in Asia were accepted by highly reputed international journals [9, 10].

A paper on the frequent use of levomepromazine was reported in a well-read Japanese journal

of psychopharmacology [11]. The use of long-acting psychotropic drug in Asia and the frequent use of the long-acting antipsychotics in Singapore were reported in British journals [12, 13].

Development of REAP

The findings presented at WPA Congress-Yokohama 2002 drew attention of many Asian psychiatrists. Japanese psychiatrists realized that Japanese patients with schizophrenia receive polypharmacy and the high-dose prescription compared with those in neighboring countries. Since 2002, REAP members organized several symposia at well-reputed international congress and presented several aspects of findings of the REAP survey. Through these interactions, the proposal was made to do the follow up survey of the prescription of schizophrenic inpatients.

The second survey was carried out in July 2004 three years after the first survey. The survey followed the same research protocol and questionnaire. A total of 2,136 cases of prescription of schizophrenic inpatients was collected from China, Hong Kong, Japan, Korea, Singapore, and Taiwan. The findings of the follow up survey were reported at a symposium of the 18th World Congress of Social Psychiatry held in October 2004 in Kobe. From 2001 to 2004, the SGAs were increased sharply in Asian countries that participated in the survey. Changing pattern from 2001 to 2004 was reported at several journals in psychopharmacology in English and Japanese [14-17].

REAP study members met and presented their data at several international meetings in Asia. Those meetings included the 12th Congress of Pacific Rim College of Psychiatrists (PRCP) held in October 2006 in Taipei, and WPA Regional Congress, September 2007 in Shanghai. Through these encounters, the third follow up of REAP survey was proposed because of a rapid change of prescription patterns for schizophrenic inpatients in many Asian countries.

Major reason for the longevity of REAP has been the pleasure of participating in the group. Many REAP study members from different countries have found it extremely rewarding to find out unique findings from the data, to write papers and make presentations at international congresses. REAP is a collection of mega data, and members could analyze them from different perspectives. Since 2008, a few journals requested REAP study members to write a review on REAP in English and Japanese [18-20].

REAP drew attention to psychiatrists from ASEAN and South Asia who attended REAP symposia at several international congresses. At the third survey in 2008, psychiatrists from India, Malaysia, and Thailand joined REAP survey. The survey on prescription of schizophrenic inpatients in 2008 was carried out in nine countries and areas in Asia (Table 1). Formerly REAP meant Research on East Asian Psychotropic Prescription Pattern. But with the admission of India, Malaysia, and Thailand to the study group, REAP has become "Research on Asian Psychotropic Prescription Pattern."

REAP Studies for Schizophrenic Patients and Antipsychotic Drugs

Symptoms of schizophrenic inpatients

Findings from REAP surveys in 2001, 2004, and 2008 were reported in many international journals in psychiatry. Singaporeans drew attention to the common use of adjunctive mood stabilizers and benzodiazepines [21, 22]. I was interested in studying symptoms and signs of schizophrenia in different countries and areas.

Table 1. Research of Asian Psychotropic Prescriptions: distribution of subjects and countries and areas

Country	2001	2004	2008
China	611	504	409
Hong Kong	108	100	100
Japan	627	583	514
Korea	442	412	284
Singapore	300	91	100
Taiwan	311	446	499
India	-	-	181
Malaysia	-	-	100
Thailand	-	-	39
Total	2,399	2,136	2,226

One of survey topics was symptoms of patients observed in the past one month. Psychiatrists in charge were asked to check the presence of symptoms in eight categories: (A) delusion, (B) hallucination, (C) disorganized speech, (D) catatonic symptoms, (E) negative symptoms, (F) decreased social and occupational function, (G-1) verbal aggression, (G-2) physical aggression, and (H) other symptoms. Data were extracted from 6,441 cases reported form China, Korea, Japan, Hong Kong, Taiwan, and Singapore in all three surveys. The most often reported symptom has been the decreased social and occupational functioning (22.15%), followed by delusion (19.65%), negative symptoms (17.63%), hallucination (16.15%), disorganized speech (8.98%), catatonic symptoms (5.9%), verbal aggression (5.65%), and physical aggression (3.86%). Interestingly, study data from six countries and areas have shown almost similar incidence of the presence of these eight symptoms among schizophrenic inpatients. In addition, the presence of these eight symptoms had also been similar throughout the surveys in 2001, 2004, and 2008. The survey showed that schizophrenic inpatients present similar psychiatric symptoms across countries, and that the pattern of psychotic symptoms had not been changed from 2001 to 2008.

Characteristic features of prescription to schizophrenic inpatients in Japan

In Japan, in the survey in 2008, 23 centers in 8 different prefectures and 68 psychiatrists participated in collecting data from 514 cases. The prescription patterns for schizophrenic inpatients differed in different centers. REAP survey in 2001 revealed the exceptional feature of the prescription of antipsychotics in Japan. Comparing with patients from other countries and areas in the collaborative survey, patients in Japan received the largest amount of antipsychotics of chlorpromazine-equivalent dose. In addition, Japan was marked with polypharmacy, and limited choices of available psychotropic drugs. In 2004, REAP survey showed the gradual decrease of the high-dose prescription (CPZ more than 1,000 mg). The average dose of antipsychotic prescription continued to decline during the REAP survey in 2008 (Figure 1). Many papers were published to caution the high-dose prescription and polypharmacy in Japan during the period from 2001 to 2008 [23, 24]. Concrete findings from REAP studies could

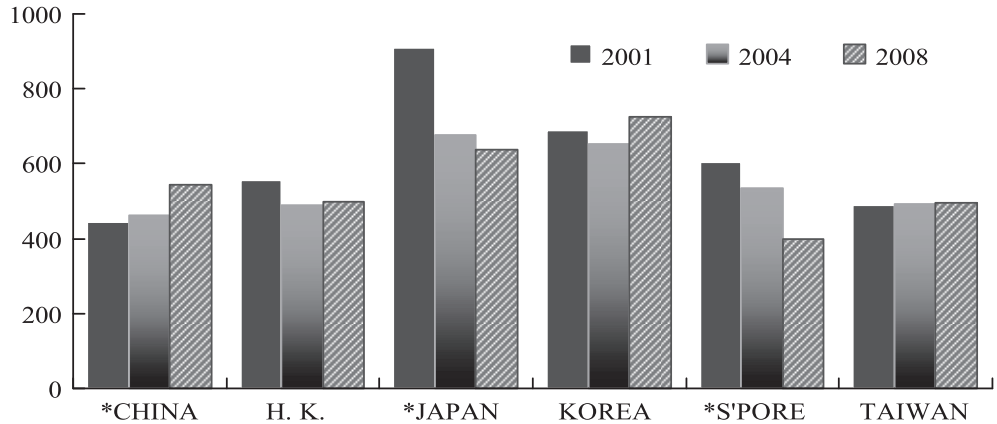

Figure1. Mean doses of antipsychotic drugs (in chlorpromazine-equivalent mg/day). *$p < 0.05$. Unit in y-axis is mg/day. H. K., Hong Kong; S'pore, Singapore.

be one of the factors contributing to reduce high-dose prescription and frequent use of polypharmacy in Japan.

From 2001 to 2008, FGAs were decreased and SGAs were increased in prescriptions in all countries and areas in REAP survey (Tables 2 and 3). In 2008, SGAs were prescribed to more than 60% of schizophrenic inpatients. The data showed the new form of the polypharmacy. Many patients received both FGA and SGA. Two kinds of SGAs have been prescribed to a certain number of patients (Table 4).

In 1997, Kazamatsuri pointed out the problematic features of the pharmacotherapy of schizophrenic inpatients in Japan [25]. They could be summarized as (A) prescription of many drugs; (B) polypharmacy of psychotropic drugs; (C) prescription of the high-dose antipsychotics for long duration; (D) frequent co-prescription of antiparkinson drugs for long duration; (E) regular prescription of hypnotics; (F) frequent prescription of high-dose laxative; as well as (G) high incidence of extrapyramidal signs, pathological thirst, polydipsia, and long lasting constipation. Three REAP surveys proved the problems pointed out by Kazamatsuri in 1997, but they were not solved in 2001, 2004 and 2008. But the introduction of SGAs contributed to lessen the side effects and to reduce the high-dose prescription of antipsychotics. Japan is reputed to have the biggest number of

Table 2. Use of top five first-generation antipsychotic drugs (FGAs), 2001-2008

FGA	2001	2004	2008
Haloperidol	690 (28.8)	387 (18.1)	412 (18.5)
Chlorpromazine	561 (23.4)	349 (16.3)	251 (11.3)
Levomepromazine	246 (10.3)	165 (7.7)	139 (6.6)
Sulpiride	232 (9.7)	178 (8.3)	129 (5.8)
Trifluoperazine	114 (4.8)	41 (1.9)	58 (2.6)

Trifluoperazine is not approved in Japan

Table 3. Use of second generation antipsychotic drugs, 2001-2008

SGA	2001 N (%)	2004 N (%)	2008 N (%)
Risperidone*	236 (9.8)	344 (16.1)	689 (30.9)
Clozapine	247 (10.3)	243 (11.4)	331 (14.9)
Olanzapine*	56 (2.3)	112 (5.2)	352 (15.9)
Quetiapine*	34 (1.4)	83 (3.9)	226 (10.2)
Aripiprazole	-	-	113 (5.1)
Zotepine	33 (1.4)	22 (1.0)	108 (4.9)
Amisulpride	-	15 (0.7)	57 (2.6)
Perospirone*	1 (0.0)	9 (0.4)	34 (1.5)
Ziprasidone	-	7 (0.3)	27 (1.2)
Blonanserin	-	-	24 (1.1)
Paliperidone	-	-	17 (0.8)

$p < 0.05$
Amisulpride, ziprasidone, paliperidone are not approved in Japan

psychiatric beds in the world both in absolute and relative term. More than 100,000 patients stay more than 5 years in psychiatric hospitals. The number of psychiatric hospitals is more than 1,600, and almost 90% of them are privately owned.

The above picture shows the uniqueness of Japanese mental health services. Likewise, REAP surveys on schizophrenic inpatients showed the unique feature of prescription pattern of psychotropics in Japan. In 2001, Murasaki stated that psychopharmacology in Japan was left behind

Table 4. Prescribing pattern of antipsychotics, 2001-2008

	2001 N (%)	2004 N (%)	2008 N (%)
Monotherapy	52%	60%	54.5%
FGA only***	601 (25.1)	409 (19.1)	209 (11.0)
SGA only***	607 (25.3)	835 (39.1)	792 (41.6)
Depot only	38 (1.6)	38 (1.8)	36 (1.9)
Polypharmacy			
FGA + SGA***	370 (15.4)	400 (18.7)	382 (20.0)
FGA + FGA***	361 (15.1)	168 (7.9)	85 (4.5)
SGA + SGA***	45 (1.9)	83 (3.9)	194 (10.2)
Depot + Depot	2 (0.1)	0	0
Depot + FGA***	274 (11.4)	103 (4.8)	64 (3.4)
Depot + SGA***	49 (2.0)	35 (1.6)	69 (3.6)
Depot +SGA + FGA	21 (0.9)	29 (1.4)	23 (1.2)

*** $p < 0.001$
FGA, first-genertion antipsychotics; SGA, second-generation antipsychotics

from the world trend for 5 to 10 years in his review on "Current stage and vision of pharmacotherapy in Japan" [26]. REAP surveys began in 2001 and could gather concrete real world data on the changes of prescription pattern of schizophrenic inpatients in Japan and in neighboring countries. REAP surveys demonstrated the differences in prescription pattern to the same clinical entities among Asian countries who participated in the surveys [27, 28].

What we have learned from REAP surveys on schizophrenic inpatients in Asia

REAP surveys have demonstrated the similar clinical features of schizophrenic inpatients in countries and areas who participated. On the other hand, the prescription pattern of psychotropic drugs to these patients differed greatly from country to country. In the past 10 years, the prescription of antipsychotics changed dramatically in all countries. The main antipsychotic drugs prescribed to schizophrenic patients were changed from FGAs in 2001 to SGAs in 2008. With this change, new form of polypharmacy, new type of co-prescription and new kinds of side effects have been observed. REAP revealed that the actual prescription has the following contributing factors: (A) national drug policy to approve new drugs in the market, (B) actual cost for a patient to pay, national insurance to cover a certain drug or not, (C) mental health service system (long-stay patients having the tendency to receive high-dose antipsychotics), and (D) side effects. In the real world, many factors are involved in the decision of the prescription behaviors. The evidence-based evaluation on the efficacy of a certain drug is one of many factors.

REAP survey in 2008 showed that SGA are the main antipsychotics for the treatment of schizophrenia in Asia. In addition, various psychotropic drugs were prescribed to schizophrenic inpatients (Table 5). To have a wide perspective on the merits and side effects of SGA is necessary in the development of services for schizophrenic patients in Asia.

Since 2010, researchers at Hong Kong Chinese University and Peking University in collaboration began writing many articles based on REAP data. They selected various aspects of interesting findings gained from REAP surveys [29-43]. Those articles have provided valuable information on the problems and challenges faced by Asian psychiatrists to develop psychopharmacotherapy for patients suffering from schizophrenia in Asia. Readers who are interested in those topics are encouraged to study those articles [29-43].

REAP Studies on Antidepressants

REAP survey on antidepressants

At the time of the International Congress of Neuro-psychopharmcology held in December 1999 in Singapore, depression was recognized as a major public health threat. *WHO World Health Report* in 1999 ranked depression as the fifth cause for the global burden of diseases [44]. Participants of the congress discussed about the epidemiology of depression in Asia. Depression had been considered less common in Asian cultures. Several members were keen to know whether the depression was on the rise in Asia, and felt that to undertake an international collaborative research on depression was necessary and fruitful. Depression defined by *ICD* and *DSM* was considered too complicated to use it as an entry point to an international collaborative survey. Also, antidepressants were commonly prescribed not only to depressive patients but also many other diseases. It took several years for researchers from dif-

Table 5. Top ten most often prescribed psychotropics for schizophrenic inpatients in six countries and areas in East Asia in 2008: Data from REAP surveys

	China	Hong kong	Japan	Korea	Singapore	Taiwan
1	Trihexyphenidyl (ANP) 146 (35.69%)	Trihexyphenidyl (ANP) 39 (30%)	Biperiden (ANP) 248 (48.24%)	Benzatropin* (ANP) 168 (59.15%)	Trihexyphenidyl (ANP) 66 (66%)	Trihexyphenidyl (ANP) 188 (37.67%)
2	Risperidone (SGA) 111 (27.13%)	Risperidone (SGA) 21 (21%)	Risperidone (SGA) 224 (43.57%)	Risperidone (SGA) 99 (34.85%)	Risperidone (SGA) 31 (31%)	Estazolam (HAS) 151 (30.26%)
3	Clozapine (SGA) 109 (26.65%)	Valproic acid (MDS) 19 (19%)	Flunitrazepam (HAS) 201 (39.10%)	Lorazepam (ANX) 97 (34.15%)	Flupentixol dec* (LNG) 27 (27%)	Clozapine (SGA) 134 (26.85%)
4	Clonazepam (MDS) 97 (23.71%)	Lithium (MDS) 16 (16%)	Levomepromazine (FGA) 139 (27.04%)	Haloperidol (FGA) 88 (30.98%)	Diazepam (ANX) 26 (26%)	Lorazepam (ANX) 114 (22.84%)
5	Olanzapine (SGA) 88 (21.51%)	Diazepam (ANX) 15 (15%)	Haloperidol (FGA) 125 (24.31%)	Valproic Acid (MDS) 69 (24.29%)	Penthixol dec* (LNG) 26 (26%)	Risperidone (SGA) 114 (22.84%)
6	Quetiapine (SGA) 83 (20.29%)	Lorazepam (ANX) 11 (11%)	Olanzapine (SGA) 121 (23.54%)	Diazepam (ANX) 42 (14.78%)	Valproic Acid (MDS) 25 (25%)	Clonazepam (MDS) 112 (22.44%)
7	Lorazepam (ANX) 44 (10.75%)	Clozapine (SGA) 11 (11%)	Valproic acid (MDS) 97 (18.87%)	Clozapine (SGA) 36 (12.67%)	Trifluoperazine (FGA) 18 (18%)	Haloperidol (FGA) 78 (15.63%)
8	Chlorpromazine (FGA) 38 (9.29%)	Zuclopenthi. dec*(LNG) 11 (11%)	Nitrazepam (HAS) 93 (18.09%)	Chlorpromazine (FGA) 34 (11.97%)	Hydroxyzine (ANX) 15 (15%)	Biperiden (ANP) 75 (15.03%)
9	Valproic acid (MDS) 33 (8.06%)	Quetiapine (SGA) 10 (10%)	Quetiapine (SGA) 83 (16.14%)	Olanzapine (SGA) 34 (11.97%)	Haloperidol (FGA) 14 (14%)	Valproic acid (MDS) 75 (15.03%)
10	Haloperidol (FGA) 27 (6.60%)	Haloperidol (FGA) 9 (9%)	Chlorpromazine (FGA) 73 (14.20%)	Clonazepam (MDS) 33 (11.61%)	Chlorpromazine (FGA) 14 (14%)	Sulpiride (FGA) 52 (10.42%)

*Not approved in Japan

FGA, first-genertion antipsychotics; SGA, second-generation antipsychotics; LNG, long-acting; ANX, anxiolytics; HAS, hypnotics and sedatives; ANP, antiparkinson drug; MDS, mood stabilizers; AND, antidepressants; dec, decanoate

ferent countries and areas to agree on the protocol and questionnaire. Finally, the agreement was reached to survey the patients receiving "antidepressants during the survey period." Fifty-six drugs were classified as antidepressants in *ATC-DDD* published annually by WHO Collaborating Center for Drug Statistics Methodology [6]. The fact that antidepressants were prescribed widely to non-depressive patients was taken into consideration. The survey was carried out from October

2003 to March 2004 in China, Korea, Japan, Taiwan, and Singapore. Researchers in five countries and areas surveyed the medical records of patients receiving antidepressants. Totally, prescriptions of 1,898 antidepressant-medicated patients were collected from China (*n* = 537), Korea (*n* = 293), Japan (*n* = 609), Singapore (*n* = 72), and Taiwan (*n* = 898).

This first large scale international survey on the prescription of antidepressants in Asia provided many interesting findings. The study showed that antidepressants have been prescribed to 61.6% of patents diagnosed as "mood disorders" (F3) based on *ICD-10* [45-49]. More than one thirds of patients receiving antidepressants have had other diagnoses such as "neurotic, stress related, and somatoform disorders" (F4), as well as schizophrenia (F2). Only 26 drugs were used in five countries and areas out of 56 antidepressants listed in *ATC-DD* [45-49]. Of top ten of the most commonly prescribed antidepressants, seven were specific serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs).

In Japan, only 5 out of 10 commonly prescribed antidepressants were available. In Korea, all 10 antidepressants were available. This limitation of the available antidepressants in Japan was due to the stringent drug policy in Japan. The drug lag has been reportedly to protect Japanese pharmaceutical companies. The situation has been improved slightly but the problem of drug lag still poses a difficult challenge to psychiatrists in Japan. Findings from the REAP survey on antidepressants in 2004 were reported by several papers both in English and Japanese [45-49].

The second survey on the prescription of antidepressants (REAP-AD2)

More than a decade has been elapsed since the first REAP meeting in Singapore in 1999. In December 2009, JSSP and NUS organized a conference in Singapore to commemorate the 50th anniversary of the Department of Pharmacology of NUS. The conference was organized jointly by the department of psychiatry of Kyushu University and the Department of Pharmacology of NUS with the title "International Conference on Depression and Suicide: Neuro-psychopharmacology and Transcultural Differences in Asia in the 21st Century."

Many REAP members participated in the conference in Singapore and discussed follow-up data of the survey on the prescription of antidepressants in 2004. Symposia at both the WPA International Congress Beijing in September 2010 and the WPA International Congress-Kaohsiung in March 2011, were another opportunities for REAP members to exchange ideas further. REAP members participated in the congresses had the extensive discussion on the research protocol of the coming survey. The survey in 2013 was agreed to follow the same inclusion criteria and questionnaire used in 2004. In addition to those, the survey in 2013 was added symptoms of depression and physical comorbidity. The survey was carried out from March to May 2013. Researchers from 10 countries and areas completed the survey and sent the data to the overall coordinator by the end of July 2013. In total, 2,320 prescriptions of antidepressants were collected from China (*n* = 350), Indonesia (*n* = 269), Hong Kong (*n* = 81), Japan (*n* = 246), Korea (*n* = 259), Singapore (*n* = 135), Taiwan (*n* = 199), India (*n* = 309), Malaysia (*n* = 161), and Thailand (*n* = 311). The tabulation and analysis of the whole data were carried out at the Taipei City Psychiatric Center. Country reports on the findings of REAP surveys in Malaysia and India were presented at the 4th World Congress of Asian Psychiatry held in August 2013 in Bangkok, Thailand. More than 1,200 psychia-

trists and mental health workers in Asia attended the Congress.

Limitations of REAP Studies

The readers are warned against over-interpreting the REAP survey findings because it has several limitations. The following limitations are some of them:

- The first limitation is that convenient samples were used without vigorous sampling process. The prescription pattern differs greatly at different institutions where the cases were collected even in the same country. One cannot exclude the sampling bias as the REAP samples are gathered mostly from the leading psychiatric centers in Asia where doctors are interested in international collaborative research. Thus, the representations of prescription are compromised to represent a given countries or area. REAP started from the curiosity to know of the common prescription pattern of psychotropic drugs in neighboring countries and areas in Asia. Therefore, REAP is the sum of many actual prescriptions at several institutions of different countries and areas in Asia. But to estimate the outline of prescription pattern is possible in a country with the certain numbers of prescriptions.
- The quality of data was not well-controlled. Research collaborators entered the prescriptions and other items to REAP questionnaire based on their own judgment. There was no previous training for standardization. The actual survey in collecting more than 6,000 prescriptions of schizophrenic inpatients was done voluntarily by participating doctors with no cost. This will limit the accuracy of the data on those items such as symptoms and side-effects. In many cases, the side effects were judged as the perceived side-effects by doctors and not the actual side-effects,
- REAP did not receive any financial supports from pharmaceutical companies. The voluntary cooperation of many Asian psychiatrists have enabled REAP to continue successfully more than 10 years. At the beginning, REAP was supported by the grant from JSSP to promote international collaboration in medical field with Singapore and with other Asian countries. In addition, Taipei City Hospital provided the fund for the data analysis. It is unlikely that REAP will continue further without receiving financial support.
- The authorship of papers is a delicate matter for REAP. The large number of names appears in the list of authorships of REAP papers because many experts from different countries made contributions. Sometimes, more than 20 names are listed in a REAP paper. The order of authors could be difficult if one starts arguing. Basically, it is the decision of the first author to decide the order. Friendship and tolerance are needed for harmonious solution in making the list of co-authors. REAP has been able to continue thanks to the friendship and tolerance of many Asian psychiatrists.

Public Health Implication in Japan

One of the important objectives of REAP has been to improve the prescriptions of psychotropic drugs in Asia. Because Japanese national insurance covers all the medical cost, prescription of many drugs to one patient is financially beneficial to a hospital. Evidenced-based medicine is powerless before the financial profit. The findings of the first survey on schizophrenic inpatients in 2001 gave an impact to Japanese psychiatrists. The con-

crete findings helped Japanese psychiatrists to understand the unique feature of psychotropic prescription pattern in Japan. The high-dose antipsychotic prescriptions and the polypharmacy of psychotropic drugs in Japan have been decreased in the past 10 years.

In February 2014, Central Medical Committee, the highest advisory board to the Ministry of Health, recommended on "the promotion of appropriate use of psychotropic drugs." The recommendation noted that "psychiatrists in Japan prescribe more polypharmacy of psychotropic drugs comparing to those in other countries." It was recommended to take necessary review to promote the appropriate prescription pattern of psychotropic drugs. The reduction of insurance cost for unneeded drugs has been proposed. To evaluate the extent the contribution of REAP to this recommendation is difficult. But we cannot ignore an impact that REAP has made to improve the prescriptions of psychotropic drugs in Japan. However, Japanese psychiatrists still have a long way to go.

Conclusion

REAP was started in 2001as a collaborative research project. Investigators from China, Hong Kong, Japan, Korea, Singapore, and Taiwan in 2001, and those from the same countries and areas participated in the REAP survey in 2004. Investigators from India, Malaysia, and Thailand joined in the survey in 2008. The survey in 2008 was carried out in nine countries and areas in Asia, and the name of REAP changed from East Asia to Asia Psychotropic Prescription Pattern. Investigators from Indonesia joined in the survey on antidepressants in 2013. As a result, REAP has more than 200 psychiatrists from 40 leading psychiatric institutions of 10 countries and areas in Asia. In the past 10 years, REAP has succeeded in forming a research network of Asian psychiatric institutions. Most of the institutions participated in REAP studies are the leading research centers in respective countries and areas. REAP group involves many eminent psychiatrists from all over Asia. Their continuous supports have enabled REAP to survive more than 10 years producing valuable scientific contributions.

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References

1. Tan C.H: New Challenges in psychopharmacology. *Singapore Med J* 2000; 41: 3-4.
2. Takahashi T, Nagamine M, Shinfuku N: Survey on the psychiatric diagnoses (ICD and DSM) in Chian,Japan, Korea and Taiwan. *Seishin Igaku* 2009; 51: 129-35 (In Japanese).
3. Zou YZ, Cui JF, Han B, et al.: Chinese psychiatrists views on global features of CCMD-III, ICD-10 and DSM-IV. *Asian J Psychiatry* 2008; 1: 56-9.
4. Inagaki A, Inada T, Fujii Y, et al.: *Dose Equivalence of Psychotropic Drugs*. Tokyo: Seiwa Syoten, 1999: 11-60 (in Japanese).
5. Woods SW: Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry* 2003; 64: 663-7.

6. WHO: ATC index with DDDs. Collaborating Center for Drug Statistic Methodology, Oslo.2000.
7. Chong MY, Tan CH, Fujii S, et al.: Antipsychotic drug prescription for Schizophrenia in East Asia: a rationale for change. *Psychiatry Clin Neurisci* 2004; 58: 61-4.
8. Fujii S, Maeda K, Shinfuku N: International collaborative studies on the prescription of antipsychotics in East Asia: finding from Research on East Asia Psychotropic Prescription Pattern. *Rinsyou Seishin Igaku* 2003: 32: 629-46 (in Japanese).
9. Sim K, Su A, Fujii S, et al.: Antipsychotic polypharmacy in patients with schizophrenia: a multicenter comparative study in East Asia. *Br J Clin Pharmacol* 2004; 58: 178-83.
10. Sim K, Su A, Leong JY, et al.: High dose antipsychotic use in schizophrenia: findings of the REAP (Research on East Asia Psychotropic Prescriptions) study. *Pharmacopsychiatry* 2004; 37: 175-9.
11. Fujii S, Shinfuku N: Historical overview on the use of levomepromazine in Japan and the setting of its dose in pharmacotherapy. *Rinsyou Seishin Yakuri* 2005; 8: 1227-38 (in Japanese).
12. Sim K, Su A, Ungvari GS, et al.: Depot antipsychotic use in schizophrenia: an East Asian perspective. *Hum Psychopharmacol* 2004; 19: 103-9.
13. Sim K, Su A, Chan YH, et al.: Clinical correlates of antipsychotic polytherapy in patients with schizophrenia in Singapore. *Psychiatry Clin Neurosci* 2004; 58: 324-9.
14. Sim K, Chuan Suh, Fujii S, et al.: Low dose of antipsychotic drugs for hospitalised schizophrenia patients in East Asia: 2004 vs. 2001. *Int J Neuropsychopharmacol* 2008; 12: 117-23.
15. Sim K, Su HC, Fujii S, et al.: High-dose antipsychotic use in schizophrenia: a comparison between the 2001 and 2004 Research on East Asia Psychotropic Prescription (REAP) studies. *Br J Clin Pharmacol* 2009; 67:110-7.
16. Yoshimura R, Okamoto T, Nakamura J, et al.: Prescription pattern of antipsychotic drugs for schizophrenic inpatients in Japan. *Psychiatry Clin Neurisci* 2006; 60: 778-9.
17. Nakano W, Yang SY, Fujii S, et al.: Characteristics of pharmacotherapy for schizophrenic inpatients in Japan: Findings from Research on East Asia Psychotropic Prescription Pattern of Antipsychotics. *Rinsyou Seishin Yakuri* 2010; 13: 103-3 (in Japanese).
18. Shinfuku N, Tan CH: Pharmacotherapy for schizophrenic inpatients in East Asia: changes and challenges. *Int Rev Psychiatry* 2008; 20: 460-8.
19. Tan CH, Shinfuku N, Sim K: Psychotropic prescription practices in East Asia: looking back and seering ahead. *Curr Opin Psychiatry* 2008; 21: 645-50.
20. Shinfuku N: Treatment of schizophrenia in East Asia. In: Ishigooka J, Okazaki Y, Higuchi T eds: *New Strategies of Treatment of Schizophrenia*. Tokyo: Sentann Igakusya, 2011: 58-66 (in Japanese).
21. Sim K, Yong KH, Chan YH, et al.: Adjunctive mood stabilizer treatment for hospitalized schizophrenia patients: Asia psychotropic prescription study (2001-2008). *Int J Neuropsychopharmacol* 2011; 14: 1157-64.
22. Tor PC, Ng TP, Yong KH, et al.: Adjunctive benzodiazepine treatment of hospitalized schizophrenia patients in Asia from 2001 to 2008. *Int J Neuropsychopharmacol* 2011; 14: 735-45.
23. Inagaki A: Polypharmacy of antipsychotics in Japan: comparaison between Japan and foreign countries. *Seishinnka Chiryougaku* 2003; 18: 771-7 (in Japanese).
24. Miyamoto S, Morokawa Y: Current situation of pharmacotherapy for schizophrenia in Japan: how to break away from poly-pharmacy and high dose prescription. *Rinsyou Seishin Yakuri* 2006; 9: 2177-87 (in Japanese).
25. Kazamatsuri H: Psychotropic drug therapy of patients in mental hospitals in Japan: the present status and problems. *Seishin Shinkei Shi* 1997; 99: 802-15 (in Japanese).
26. Murasaki M: Current situation and prospect of psychopharmacotherapy in Japan: toward the 21st century. *Rinsyou Seishinn Yakuri* 2001: 4: 3-27 (in Japanese).
27. Ito H, Okumura Y, Higuchi T, et al.: International variation in antipsychotic prescribing for schizophre-

nia: pooled results from the research on East Asia psychotropic prescription (REAP) studies. *Open Journal of Psychiatry* 2012; 2: 340-6.

28. Nakano W, Fujii S,Shinfuku N, et al.: Changes of prescription pattern for schizophrenic inpatients in Asia over the past 10 years finding from Research on Asian Psychotropic Prescription Pattern. Rinsyou Seishinn Yakuri 2011; 14: 1397-411 (in Japanese).
29. Xiang YT, Wang CY, Si TM, et al.: Sex differences in use of psychotropic drugs and drug-induced side effects in schizophrenia patients: findings of the Research on Asia Psychotropic Prescription (REAP) studies. *Aust N Z J Psychiatry* 2010; 45: 193-8.
30. Xiang YT, Wang CY, Si TM, et al.: Use of anticholinergic drugs in patients with schizophrenia in Asia from 2001 to 2009. *Pharmacopsychiatry* 2011; 44: 114-8.
31. Xiang YT, Wang CY, Si TM, et al.: Tardive dyskinesia in the treatment of schizophrenia: the findings of the Research on Asian Psychotropic Prescription Pattern (REAP) survey (2001-2009). *Int J Clin Pharmacol Ther* 2011; 49: 382-7.
32. Xiang YT, Wang CY, Si TM, et al.: The low frequency of reported sexual dysfunction in Asian patients with schizophrenia (2001-2009): low occurrence or ignored side effect? *Hum Psychopharmacol* 2013: 26: 352-7.
33. Xiang YT, Wang CY, Si TM, et al.: Clozapine use in schizophrenia: findings of the Research on Asia Psychotropic Prescription (REAP) studies from 2001 to 2009. *Aust N Z J Psychiatry* 2011; 45: 968-75.
34. Xiang YT, Wang CY, Si TM, et al.: Antipsychotic Polypharmacy in Inpatients with Schizophrenia in Asia (2001-2009). *Pharmacopsychiatry* 2012; 45: 7-12.
35. Xiang YT, Kreyenbuhl J, Dickerson FB, et al.: Use of first- and second-generation antipsychotic medications in older patients with schizophrenia in Asia (2001-2009). *Aust N Z J Psychiatry* 2012;46: 1159-64.
36. Xiang YT, Dickerson F, Kreyenbuhl J, et al.: Common use of anticholinergic medications in older patients with schizophrenia: findings of the Research on Asian Psychotropic Prescription Pattern (REAP) study, 2001-2009. *Int J Geriatr Psychiatry* 2013; 28: 305-11.
37. Xiang YT, Kreyenbuhl J, Dickerson FB, et al.: Antipsychotic treatment in older schizophrenia patients with extrapyramidal side effects in Asia (2001-2009). *Int J Clin Pharmacol Ther*. 2012; 50: 500-4.
38. Xiang YT, Dickerson F, Kreyenbuhl J, et al.: Prescribing patterns of low doses of antipsychotic medications in older Asian patients with schizophrenia, 2001-2009. *Int Psychogeriatr* 2012; 24: 1002-8.
39. Xiang YT, Dickerson F, Kreyenbuhl J, et al.: Adjunctive mood stabilizer and benzodiazepine use in older Asian patients with schizophrenia, 2001-2009. *Pharmacopsychiatry* 2012; 45: 217-22.
40. Xiang YT, Dickerson F, Kreyenbuhl J, et al.: Common use of antipsychotic polypharmacy in older Asian patients with schizophrenia (2001-2009). *J Clin Psychopharmacol* 2012; 32: 809-13.
41. Xiang YT, Buchanan RW, Ungvari GS, et al.: Use of clozapine in older Asian patients with schizophrenia between 2001 and 2009. *PLoS One* 2013; 8: e66154.
42. Xiang YT, Ungvari GS, Wang CY, et al.: Adjunctive antidepressant prescriptions for hospitalized patients with schizophrenia in Asia (2001-2009). *Asia Pac Psychiatry* 2013; 5: E81-7.
43. Xiang YT, Li Y, Correll CU, Ungvari GS: Common use of high doses of antipsychotic medications in older Asian patients with schizophrenia (2001-2009). *Int J Geriatr Psychiatry* 2013, in press.
44. Shinfuku N, Wang XD, Chen T: Epidemiology of mood disorders from an international perspective: with special reference to Asian countries. *Singapore Med J* 2000; 41: 10-5.
45. Fujii S,Kaneko N, Kitsukawa H, et al.: Prescription of antidepressants in Japan: finding from international collaboratinve study on the prescription of antidepressantgs in five countreis and aeas in Asia. *Japanese Journal of Social Psychiatry* 2005; 14: 30-5 (in Japanese).
46. Sim K, Lee NB, Chua HC, et al.: Newer antidepressant drug use in East Asian psychiatric treatment settings: REAP (Research on East Asia Psychotropic Prescriptions) Study. *Br J Clin Pharmacol* 2007; 63: 431-7.
47. Tanaka M, Nagai H, Uchida N, et al.: Current situa-

tion on the prescription of antidepressants in East Asia: findings from REAP collaborative surveys in five countries and areas. *Rinsyouseishin Yakuri* 2007; 10: 131-46 (in Japanese).

48. Uchida N, Chong MY, Tan CH, et al.: International study on antidepressant prescription pattern at 20 teaching hospitals and major psychiatric institutions in East Asia: Analysis of 1898 cases from China, Japan, Korea, Singapore and Taiwan. *Psychiatry Clin Neurosci* 2007; 61: 522-8.
49. Shinfuku N: Pharmacotreatment of depression in East Asia. Edited by Kanba S, Kuroki T, eds: *Clinics of Depression at Present*, Tokyo: Sougen-sya, 2009: 42-59 (in Japanese).