

RESEARCH PROPOSAL

Title :

Research on Asian Psychotropic Prescription Patterns (REAP): Prescribing Pattern for Patients with Schizophrenia in Asia

Abbreviation: **REAP-AP3**

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ABSTRACT

The most common therapeutic intervention in medicine is the writing of a prescription. It is especially true in psychiatry as pharmacotherapy has become its mainstay treatment. A review of literature on psychopharmacological studies revealed that there were great discrepancies of reported rates for psychotropic drug utilization patterns. As more and more new psychotropic agents are introduced into the market, it is necessary to assess the prescribing patterns and their change over time.

In the first psychopharmacological survey of prescription patterns of antipsychotics for schizophrenia in six East Asian countries and regions in 2001 (the REAP-AP1), it was found that the second-generation antipsychotic drugs (SGA) was generally under-utilized; Japan had a relatively higher dose and antipsychotic polypharmacy, Singapore had a high utilization of depot injections while China had a higher prescription of clozapine. The use of SGA was targeted at the alleviation of positive, negative psychotic symptoms as well as disruptive behavior in schizophrenia, while the conventional or first-generation antipsychotics (FGA) were mainly used for controlling aggressive behavior. A phase-II survey was undertaken in 2004 (REAP-AP2) and was found to have the trend of increasing tendency use of SGA with reciprocal decreasing use of FGA among the East Asian countries.

This phase-III international collaborative study (REAP-AP3), with more participating centers covering larger part of Asia, aims to continue the investigation of psychotropic prescription patterns, focusing on their change over time, determinants and predictors of use of antipsychotic drugs for schizophrenia in Asia, and to analyze factors that affect these changes. Collaborative centers include psychiatric institutes or centers from China, Hong Kong, India, Japan, Korea, Singapore, Taiwan and Thailand. The design is a cross-sectional psychopharmacoepidemiological survey of prescription patterns for patients with schizophrenia admitted for treatment from 1st to 30th of October, 2008. Data collection will be conducted in a standardized protocol that will include patients' social and clinical characteristics, psychiatric symptoms, course of illness, and information about medications including types of drugs, dosages and adverse effects.

Rates and types of prescribing antipsychotic drugs will be estimated, with comparison of the change and trend, and to test their differences between countries or region applying Chi-square tests. Doses of antipsychotic drugs will be compared using t-tests or analysis of variance. Multiple logistic regression analyses will apply to assess the independent and interactive effect of various factors that could affect the choice of prescribing FGA or SGA. Each sociodemographic and clinical variable will be included in the initial analyses, and only the significant variables in the univariate analyses will be included as independent variables to find the model of best fit. The results could contribute to better understanding of psychotropic drugs utilization in Asia, further to suggest ways to improve prescription habits.

GENERAL INTRODUCTION

When prescribing a drug, psychiatrist nowadays is facing a wide variety of psychotropic medications to choose. Most official guidelines on recommendations of the use of psychotropic drugs are mainly based on randomized controlled trial findings and routine conditions, while good prescribing practice principally emphasized not only on appropriateness and effectiveness, but also safety and cost [Parish, 1973].

Studies have shown that large differences exist between the conditions of pre-marketing clinical trials and those of the actual practice several years into the market life of a pharmaceutical product [Martin *et al*, 2004]. In pre-marketing clinical trial, a small sample of people was selected from the source population by inclusion and non-inclusion criteria in order to reduce inter-individual variability. These people are usually treated with a fixed protocol, specifying dosage, duration and concomitant medications [Verdoux & Begaud, 2004]. In actual clinical practice, however, clinicians often use drugs in ways that are not studied in pre-marketing trials; they may prescribe the drug to different groups of patients, use different treatment regimens, and even accept different indications for therapy (off-label use). In spite of this, prescribing behavior is affected by a variety of factors, apart from physician and patients, including socio-economic and health delivery systems as well as the promotion of pharmaceutical companies [Hemminki, 1988].

Since the discovery of chlorpromazine in the early 1950's, psychotropic drugs are now among the most widely prescribed medications in general medicine as well as psychiatric populations. Antipsychotic drugs have proved to be effective in the treatment of schizophrenia [Kane, 1994], a severe debilitating disorder that typically begins in the late adolescent or early adult. Two groups of antipsychotic drugs are currently used to treat schizophrenia: the conventional drugs comprised of chlorpromazine and its derivatives, so called First Generation Antipsychotics (FGA), and the novel or atypical antipsychotics (the Second Generation Antipsychotics, SGA). The FGA are relatively inexpensive, but could induce higher tendency of adverse effects in extra-pyramidal and other symptoms than the SGA. In order to improve drug therapy, drug utilization data from the postmarketing period are important and essential.

Drug utilization as defined by the World Health Organization (WHO) as the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economical consequences [WHO, 1977]. It varies among geographical regions and with time. A review of literature on psychotropic drug utilization studies revealed that there were great discrepancies of reported rates for antipsychotic drug utilization patterns for schizophrenia across Europe [Bowers *et al*, 2004], America [Rothbard *et al*, 2003] and Asia [Chong *et al*, 2004]. Under-utilization of the second-generation antipsychotic drugs (SGA) was generally found, and also differed among different countries and regions. In the East-Asian study, for example, it was found that Japan had a relatively higher dose and antipsychotic polypharmacy, Singapore had a high utilization of depot injections while China had a higher prescription of clozapine. High prescription of clozapine was observed in China with relatively very low utilization of other atypicals because of their availability and costs. The cost of clozapine is approximately 40-fold higher in Singapore or Taiwan than in China. Chong *et al* (2004) found that the use of SGA was targeted at the alleviation of positive, negative psychotic symptoms as well as disruptive behavior in schizophrenia, while the conventional or first-generation antipsychotics (FGA) were mainly used for controlling aggressive behavior.

Drug utilization data alone cannot explain whether such use of drug in a community or population is excessive, inadequate, or inappropriate. It can only demonstrate the trend of drug usage or factors affecting the drug exposure in the studied population. Cautious interpretation of the results is noteworthy as drug utilization is primarily depending on the availability of the drugs of the studied population, drug regulatory system, health delivery system, the consumer, cost and marketing of pharmaceutical company, and other factors [Hemminki, 1975; Christensen & Bush, 1981]. Drug utilization studies, with objectives of problem identification and problem analysis [Lunde & Baksaas, 1988], are primarily quantitative studies of descriptive epidemiology. They address the relationship between therapeutic practice and actual clinical practice [Lasgna, 1974] and to identify discrepancies between guidelines based on clinical trials and actual use. Such kind of studies is still inadequate in Asia and in many developing countries.

BACKGROUND OF THE PROJECT

In December 1999, National University of Singapore (NUS) and Japan Society for Promotion of Science (JSPS) coordinated and organized an International Symposium on New Challenges of Neuropsychopharmacology in Singapore. Feeling the need to understand the prescribing behavior in Asian countries, an international collaborative research group was formed. The group (REsearch on east-Asia Prescribing pattern, REAP) comprised of psychiatrists, pharmacologists, epidemiologists and pharmacoconomists, held several research meetings and conducted 2 major studies on the utilization of antipsychotics for the treatment of schizophrenia in 2001 (REAP-AP1) and 2004 (REAP-AP2), and another one on the use of antidepressants (REAP-AD1) among 8 East-Asian regions and countries (China, Hong Kong, Indonesia, Japan, Korea, Malaysia, Singapore and Taiwan). The whole project was supported by research funds from the (1) Japan Society for Promotion of Science, Japan (2) International Center for Medical Research, Kobe University, School of Medicine, Japan (3) Bureau of National Health Insurance, Taiwan (DOH92-NH-1025) (4) Chang Gung Memorial Hospital, Taiwan (CMRPG83043), and (4) Institute of Mental Health, Singapore (Project 013/2001).

Findings of the collaborative research were reported at the national and international conferences, and to date, a total of 13 papers (7 in English 6 in Japanese) were published (Appendix 1). Excerpts of some publications involving 2,399 cases of the REAP-AP1 study are summarized as follows:

1. Chong MY, Tan CH, Fujii S, Yang SY, Ungvari G, Si T, Chung EK, Sim K, Shinfuku, N (2004). Antipsychotic drug prescription for Schizophrenia in East Asia: A rationale for change. *Psychiatry and Clinical Neurosciences* 58 (1), 61-67.

This international collaborative study aimed to study the prescription patterns of antipsychotic drugs for schizophrenia in East Asia and to analyze factors that affect these patterns. Prescription patterns for patients admitted for treatment of schizophrenia were surveyed using a standardized protocol from 6 East Asian region/countries: China, Hong Kong, Japan, Korea, Singapore and Taiwan. Patients' social and clinical characteristics, psychiatric symptoms, course of illness, and adverse effects of medications were systematically assessed and recorded. Prescriptions of the first and second generation antipsychotic drugs were compared. Altogether, 2,399 patients were recruited. The second generation drugs comprised 28.1% of all prescribed antipsychotics, and 46% of the antipsychotic prescriptions were in the context of polypharmacy. The mean dosage of antipsychotics for the whole sample was 675.3 ± 645.1 mg CPZ eq. Japan had a relatively higher dose and antipsychotic polypharmacy; Singapore had a high utilization of depot injections while China had a higher prescription of clozapine. Using multiple logistic regression analysis, distinctions in the prescription patterns of antipsychotic drugs were found: first generation drugs were mainly for controlling aggressive behavior, while second generation drugs were targeted at the alleviation of positive, negative psychotic symptoms as well as the disruptive behavior in schizophrenia. This collaborative study highlighted differences in the prescription patterns especially the under-utilization of second-generation antipsychotic drugs in East Asia. The pattern of antipsychotic medication use varied from country to country and is likely to be influenced by the prevailing health care system, the availability and costs of the drugs.

2. Sim K, Su A, Fujii S, Yang SY, Chong MY, Ungvari GS, Si T, Chung EH, Tsang HY, Chan YH, Heckers S, Shinfuku N, Tan CH (2004). Antipsychotic polypharmacy in patients with schizophrenia: A multicentre comparative study in East Asia. *British Journal of Clinical Pharmacology* 58 (2), 178-183.

Previous studies on the prescription patterns of psychotropic medications in patients with schizophrenia have highlighted a high rate of antipsychotic polypharmacy but the data in Asia are sparse. This study seeks to examine the prevalence of antipsychotic polypharmacy in patients with schizophrenia and compare the differences between patients receiving one versus more than one antipsychotic. Antipsychotic prescription for a sample of 2399 patients with schizophrenia from six countries and territories were evaluated. Daily doses of antipsychotic medications were converted to standard chlorpromazine equivalents. Antipsychotic polypharmacy was found in 45.7% (n=1097) of the patients with wide inter-country variations. Polypharmacy was associated with male gender (OR 1.24, 95%CI 1.06-1.46, p<0.01), advanced age (t=-7.81, df=2396, p<0.001), multiple admissions (OR 1.33, 95%CI 1.06-1.67), psychiatric hospital setting (OR 1.34, 95%CI 1.11-1.62) as well as higher daily CPZeq dosage (411.47 versus 983.10 CPZ eq/d, z=-25.94, p<0.001), anticholinergic use (OR 3.17, 95%CI 2.65-3.79, p<0.001) and less use of atypical antipsychotic (OR 0.83, 95%CI 0.71-0.98, p<0.05). On multivariate analysis, country, age and duration of illness were significantly associations with antipsychotic polypharmacy. This exploratory study highlighted the wide inter-country variations of this prescription trend which is likely to be influenced by a complex combination of clinical, setting, cultural and personal practice factors, requiring further research.

3. Sim K, Su A, Ungvari G, Fujii S, Yang SY, Chong MY, Si T, Chung EK, Tsang HY, Chan YH, Shinfuku N, Tan CH (2004). Depot antipsychotic use in schizophrenia: an East Asian perspective. *Human Psychopharmacology* 19 (1), 103-109.

Depot antipsychotic medication was first developed in the 1960s and still has an important place in the pharmacotherapy of patients with psychotic illnesses such as schizophrenia. Few studies have examined its use in Asian patients with schizophrenia. This international, multi-centre, cross-sectional study examined the prevalence of depot antipsychotic use and compared the socio-demographic and clinical characteristics of patients receiving and not receiving depot antipsychotic medication. Across six East Asian countries, territories and 32 centres, antipsychotic use in 2,399 patients with schizophrenia were surveyed using a standardized protocol. Dosages of antipsychotic drugs were converted to chlorpromazine equivalents. Depot antipsychotic medications were prescribed in 15.3% (n=368) of the patients, being the most common in Singapore, followed by Taiwan, Japan and China. Being on depot antipsychotic drugs was significantly associated with a younger age in Japan (t=2.13, df=625, p<0.05), male gender (particularly in Taiwan and Japan, p<0.05), delusions in Japan (OR=2.19, 95% CI 1.08-4.45, p<0.05), aggression (p<0.01), higher daily total CPZ equivalent dose (z=-7.33, p<0.001) and co-prescription of anticholinergic drugs (OR 3.6, 95% CI 2.7-4.8, p<0.001). Patients on depot antipsychotic medications were less likely to have disorganized speech (particularly in China, OR=0.25, 95% CI 0.09-0.71, p<0.01) and negative symptoms (particularly in Japan and Singapore, p<0.05). In a multiple logistic regression model, several factors including country, younger age, longer duration of illness and the lack of use of oral, atypical antipsychotic drugs were found to be

significantly associated with depot antipsychotic use. There was a wide variation in the prevalence of depot antipsychotic prescription across countries in South-East Asia. The results suggest that the prescription of depot antipsychotics is not guided by any recognizable principles and more likely determined by local traditions and personal choices. There is a need to re-examine the risk-benefit profile of each patient before deciding on the initiation or continuation of depot antipsychotic medication.

4. Sim K, Su A, Leong JY, Yip K, Chong MY, Fujii S, Yang SY, Ungvari GS, Si T, Chung EK, Tsang HY, Shinfuku N, Kua EH, Tan CH (2004). High dose antipsychotic use in schizophrenia: Research on East Asia Psychotropic Prescription (REAP) findings. *Pharmacopsychiatry* 37 (4), 175-179.

The most appropriate dose of antipsychotic drugs used in the management of patients with schizophrenia is still being debated. High-dose regimes (defined as more than 1000 chlorpromazine-equivalents (CPZeq) milligrams per day) are not uncommon, but most reports are from western countries. Recent functional neuroimaging studies have found that the previous notion concerning the use of antipsychotic medication, especially in high doses, was unsupported and untenable. This international study examined the use of high dose antipsychotic medication and its clinical correlates in East Asian schizophrenia patients. Prescription patterns for inpatients with schizophrenia from six countries and territories (China, Hong Kong, Japan, Korea, Taiwan, and Singapore) were studied. Within the study group (n=2399), 430 patients (17.9%) were prescribed high dose antipsychotics. Antipsychotic use varied significantly between countries, with Japan, Korea, and Singapore using higher doses than the other countries. High dose antipsychotic use was associated with younger age in Japan ($p<0.001$), longer duration of admission ($p<0.001$), duration of illness ($p<0.001$, particularly in Korea and Taiwan), positive psychotic symptoms ($p<0.001$, particularly in Japan and Korea), and aggression ($p<0.05$, particularly in Japan), and also with a higher likelihood of extrapyramidal and autonomic adverse effects ($p<0.05$, particularly in China). Country, younger age, the presence of delusions and disorganized speech, polypharmacy, and receiving depot medication but not atypical antipsychotic drugs were important predictors of high antipsychotic use. This survey revealed that high antipsychotic dosing is not an uncommon practice in East Asia. It behooves prescribing clinicians to constantly reevaluate the rationale for such a practice.

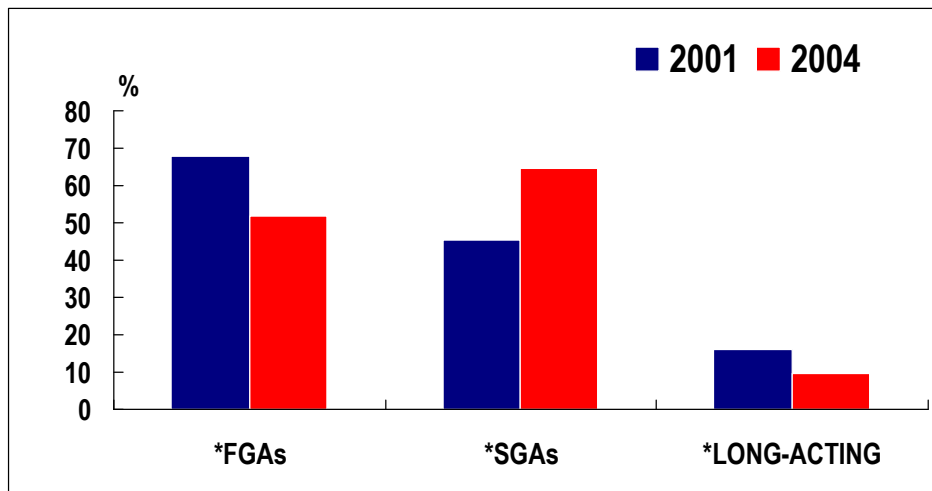
Three years after the first survey, a follow-up survey (REAP-AP2) was conducted, relying on the existing research network and enlarging it by including more centers and more countries from the region. Altogether, 2136 patients were assessed by 204 psychiatrists in 25 centers of the 6 countries and region. There were no much differences of the characteristics of samples between the REAP-AP1 and REAP-AP2 survey, except in the REAP-AP2 survey, there were more weight gain and less longer hospitalized days among the studied subjects.

However, the pattern of prescribing antipsychotic changed, as can seen from Table 1 and Figure 1 that there was a trend of increasing use of SGA with reciprocal decrease use of FGA.

Table 1. Comparison of the utilization pattern of antipsychotics for schizophrenia in East Asia between 2001 and 2004

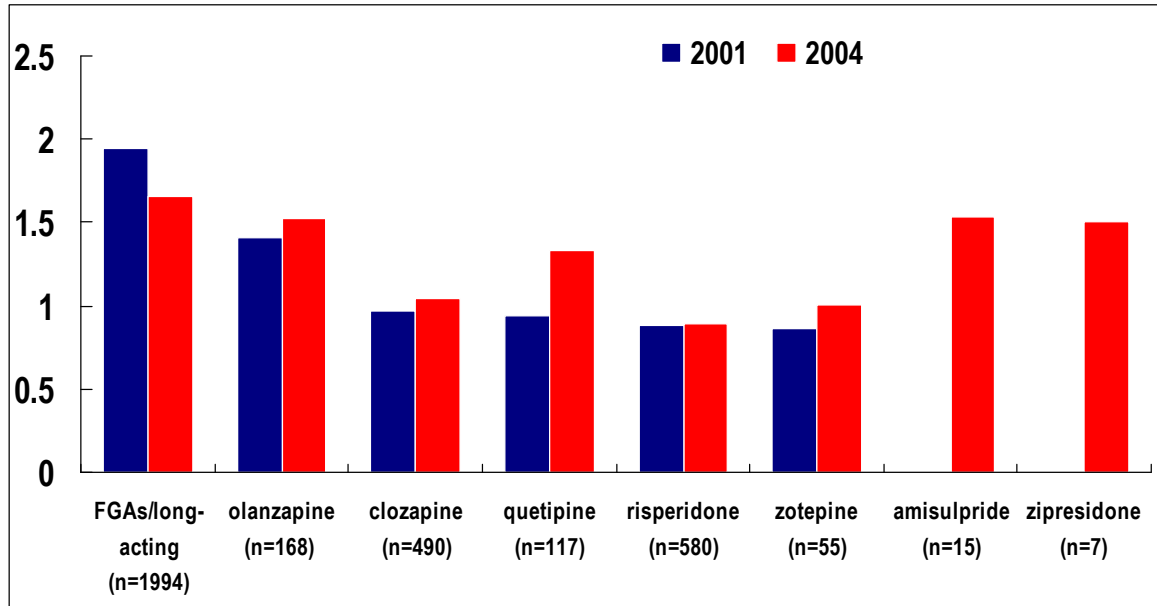
N (%)	2001	2004	Total
Monopharmacy			
FGA only*	639 (25.3)	447 (17.7)	1086 (23.9)
SGA only*	607 (24.0)	835 (33.0)	1442 (31.8)
Polypharmacy			
FGA + FGA*	637 (32.8)	271 (14.0)	908 (20.0)
SGA + SGA *	45 (2.3)	83 (4.3)	128 (2.8)
FGA + SGA*	440 (22.7)	464 (23.9)	904 (19.9)

Figure 1. Comparison of antipsychotics used between 2001 and 2004



When dosage was analyzed using the DDD/PDD ratios, it was found that most SGA were expected to have higher doses of need following the years.

Figure 2. Comparison of the PDD/DDD ratios of SGAs used in East Asia between 2001 and 2004



Summary of the findings from the studies of REAP-AP1 and REAP-AP2 surveys:

1. Prescription patterns of antipsychotic drugs for the treatment of schizophrenia greatly differed between East Asian countries. The variations were largely accounted for by the differences in these countries or region respective healthcare policies (Japan and Taiwan), preferred treatment modality like the use of depot (Singapore) or polypharmacy (Japan), and the availability and costs of the drugs (China).
2. The rationale for using conventional antipsychotic drugs was merely for controlling aggressive behavior. The SGA were targeted at the alleviation of positive, negative psychotic symptoms as well as disruptive behavior in schizophrenia.
3. There was a general under-utilization of SGA, but the trend of using the SGA was increasing following the years with reciprocal decreasing use of FGA.
4. Antipsychotic polypharmacy is a widely variable and prevalent prescribing practice in the management of patients with schizophrenia within East Asia. Antipsychotic polypharmacy in Japan was largely due to the combination of first and second generation drugs. There is likely a complex interplay of factors influencing this prescription trend including clinical, social, cultural and setting factors.
5. There were wide variations in prevalence of high dose antipsychotic use between East Asian countries, with Japan (36.5%) having almost ten times the prevalence rate of Hong Kong (3.7%). In general, patients with schizophrenia in East Asia, except Japan, received relatively lower doses of antipsychotics than their Caucasian counterparts, a finding that is compatible with other studies. The administration of higher doses of antipsychotics used in Japan might be related to polypharmacy that were commonly observed in that country.

Large-scale surveys of prescribing patterns are often difficult to conduct, especially involving countries with different socio-cultural traditions and health care systems. Most psychopharmacoepidemiology studies were conducted in European or North America, and there were very few conducted in Asia. Based on the above findings from REAP-AP1 and REAP-AP2 studies, this project aims to further study the trend and change of psychotropic drugs utilization by extending study samples to cover more representative regions in Asia, including South Asia and Indochina.

SPECIFIC AIMS

The aims of this project are to assess the utilization and impact (benefit and risk in 'real life' conditions) of psychotropic drugs for the patients who were treated for schizophrenia, further to suggest ways to improve the prescribing habits of Asian psychiatrists.

Objectives are:

1. To study psychotropic drugs utilization and their changes in Asian countries.
2. To analyze factors affecting utilization pattern of psychotropic drugs in the participating countries.
3. To evaluate the impact of prescription habits in each of the participating countries.
4. To suggest ways to improve prescription habits of psychotropic drugs in the participating countries.

RESEARCH DESIGN AND METHODS

The design of this project is a quantitative study of descriptive epidemiology. Data will be collected on a unified protocol (Appendix 3) by the psychiatrists of the participating centers. Cases with schizophrenia admitted for treatment at a single month of a year will be recruited. The prescribing habits of psychiatrist will be analyzed, taking consideration of the available psychotropic drugs on the market and different geographical and practicing system. It attempts to answer questions regarding the disparity between therapeutic practice and actual clinical practice.

Drug Exposure

(a) Classification of drugs

The WHO Anatomic Therapeutic Chemical (ATC) system will be used to classify the drug classification system in this study. The drugs to be investigated in this project are psychotropic drugs, and fall into the category of psychoactive drugs by the ATC classification system [WHO, 1998; 2002]. It consists of five hierarchical levels: a main anatomical group, two therapeutic subgroups, a chemical-therapeutic subgroup and a chemical substance subgroup. Psychotropic drugs for example, were categorized in such system included antipsychotics (N05A: FGAs, SGAs, and depot antipsychotics), antidepressants (N06A), antiepileptics and lithium (or mood stabilizers, N03A and N05AN), anxiolytics (N05B), hypnotics and sedatives (N05C), and anti-parkinson drugs (N04) [Shiloh et al, 2000].

The ATC classification system is useful for reporting drug consumption statistics and conducting comparative drug utilization research. The WHO international Drug Monitoring Program uses the system for drug coding in adverse drug reaction monitoring. Many countries also employ the ATC system to classify their essential drugs.

(b) Units of Measurement

Drug exposure, in pharmacoepidemiology terms, is the dosing regimen, with population perspective, focusing on the times of dosing. To estimate the population drug exposure, we will employ technical units of comparison using the defined daily dose (DDD) and prescribed daily dose (PDD). The DDD is the assumed average maintenance dose for the main indication of a particular drug [WHO, 1996; 1998; 2002], while the PDD is the average daily dose prescribed, as obtained from a representative sample of prescriptions.

To make crude estimates of the number of persons exposed to a particular drug or class of drugs, we calculate each prescribed daily dose (PDD) by averaging total dose in the admission over the length of stay in days and compared with those suggested in the WHO DDD assignment. The method has been useful in describing and comparing patterns of drug utilization [Bergnab et al, 1979; Yang et al, 2006], providing denominator data to estimate adverse drug reaction rates [Bergman et al, 1978], performing epidemiological screening for problems in drug utilization [Westerholm, 1986], and could monitoring the effects of informational and regulatory activities.

Samples

Patients admitted for treatment of schizophrenia will be recruited for the study. The inclusion criteria are:

- (a) Diagnosis of schizophrenic disorders according to the DSM-IV criteria (APA, 1994) or the ICD-9-CM Classification of Mental and Behavioral Disorder (WHO, 1992).
- (b) Admission to inpatient treatment from Oct 1 to 30, 2008
- (c) Comply to the study

Exclusion criteria are:

- (a) Refuse or not comply to the study
- (b) Other serious physical co-morbidity

Sample size: 100 patients from each center, 300 from each country (Japan, China and India: 600)

Participating Centers

Centers agreed for participating in the project are:

1. China: centers from Beijing, Shanghai, Changsha and Chengdu
2. Hong Kong, SAR, China: Chinese University of Hong Kong
3. India: Lucknow, Bangalore, Chandigarh, Mumbai, Trichur, Guwahati and Ranchi
4. Japan: Saga, Fukuoka, Okayama, Kobe, Tokyo and Sendai
5. Korea: Seoul
6. Singapore: National University of Singapore, Institute of Mental Health
7. Taiwan: Kaohsiung, Taipei, Hualian, Tainan
8. Thailand: Bangkok, Songka

Obligation of Each Participating Country

1. To gather data for at least 100 in-patients with the diagnosis of schizophrenia for each center.
2. To enter the data into the prescribed form, and using the computer software provided.

Target Survey Dates

Oct 1, 2008 to Oct 30, 2008

Data analysis

(a) General characteristics of samples

Sociodemographic and clinical characteristics of the sample will be first described and examined using Chi-square tests for categorical variables and t-tests or analysis of variance for their means.

(b) Drug exposure

The rates of prescribing antipsychotic drugs were then calculated, and will be tested against their differences between countries or region. Utilization pattern of drugs were analyzed, with comparing types of drugs and dosage, its trend and change over time.

A PDD/DDD ratio for every patient was calculated to represent the relative amount of dosage. If the patient's PDD corresponded exactly to the DDD, then assigned PDD/DDD ratio would be defined as 1. The greater of number above 1, the higher the dosage. In another word, the lower of number below 1, than the lower the dosage.

(c) Prediction models for prescribing pattern

Models for prediction of the prescribing pattern of psychotropic drugs will be performed, with multiple logistic regression analyses. Each sociodemographic and clinical variable will be included in the initial analyses, and only the significant variables in the univariate analyses will be included as independent variables to find the model of best fit.

ANTICIPATED RESULTS

This collaborate project on the investigation on the utilization of psychotropic drugs in schizophrenia in Asia will provide a better understanding in psychopharmacological treatment of schizophrenia. Wide variation of antipsychotics used will still be expected across the countries and regions, taking considerations of various factors that could influence the utilization of drugs. However, progress in prescribing habits is also to be expected, with improving in rationale and the use of SGA. The results of the project could contribute to the publication in international and domestic journals, while findings will contribute as solid evidence to generate programs to improving prescribing habits of Asian psychiatrist.

HUMAND SUBJECTS AND POTENTIAL HAZARDS

This proposed project does not involved in the experimental trials or laboratory investigations of the subjects, and thus will not pose any physical hazard to the study subjects concerned.

However, strict confidentiality of the data available will be observed.

REFERENCES

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorder, 4th Edition. Washington DC: American Psychiatric Press, 1994.
2. Bergman U, Boman G, Wiholm BE: Epidemiology of adverse drug reactions to phenformin and metformin. *Br Med J* 1978;2:464-6.
3. Bergnab U, Grimsson A, Wahba AHW, Westerholm B: *Studies in Drug Utilization (Europeran Series 8)*. Copenhagen: WHO Regional Office for Europe, 1979.
4. Bowers L, Callangan P, Clark N, Evers C: Comparisons of psychotropic drug prescribing patterns in acute psychiatric wards across Europe. *Eur J Clin Pharmacol* 2004;60:29-35.
5. Chong MY, Tan CH, Fujii S, Yang SY, Ungvari G, Si T, Chung EK, Sim K, Shinfuku N: Antipsychotic drug prescription for Schizophrenia in East Asia: A rationale for change. *Psychiat Clin Neuro* 2004;58 (1):61-7.
6. Christensen DB, Bush PJ: Drug prescribing: Pattern, problems and proposals. *Soc Sci Med* 1981;15:343-55.
7. Lunde PKM, Baksaas I. Epidemiology of drug utilization - basic concepts and methodology. *Acta Med Scand Suppl* 1988;721:7-11.
8. Hemminki E: Review of literature on the factors affecting drug prescribing. *Soc Sci Med* 1975; 9:111-15.
9. Hemminki E: Factors influencing prescribing. In: Ghodse H, Khan I eds. *Psychoactive Drugs: Improving Prescribing Practices*. Geneva: WHO, 1988:22-35.
10. Hennessy S, Strom BL, Lipton H, Soumerai SB. Drug utilization review. In: Strom BL: *Pharmacoepidemiology (Third Edition)*. Chichester: John Wiley and Sons Ltd, 2000:505-23.
11. Kane JM, Freeman HL: Towards more effective antipsychotic treatment. *Br J Psychiatry* 1994;165 (suppl 25):22-31.
12. Lasgna L: A plea for the naturalistic study of medicines. *Eur J Clin Pharamcol* 1974;7:153-4.
13. Maj M, Sartorius N: *Schizophrenia 2nd ed*. Chichester:John Wiley. England. 2002.

14. Martin K, Begaud B, Latry P: Differences between clinical trials and post-marketing use. *Brit J Clin Pharmacol* 2004;57:86-92.
15. Parish, P: Drug prescribing – the concern of all, *J Roy Soc Health* 1973;4: 213–7.
16. Rothbard AB, Kuno E, Foley K: Trend in the rate and type of antipsychotic medications prescribed to persons with schizophrenia. *Schizophr Bull* 2003;29(3):531-40.
17. Shiloh R, Nutt D, Weizman A. *Atlas of psychiatric pharmacotherapy*. Revised edition 2000. Martin Dunitz. London, UK. 2000.
18. Verdoux H, Begaud B: Pharmaco-epidemiology: what do (and don't) we know about utilization and impact of psychotropic medications in real-life situations? *Br J Psychiatry* 2004;185:93-94.
19. Westerholm B. Therapeutic auditing at the national and international level. *Br J Clin Pharmacol* 1986;22:555-98.
20. WHO Expert Committee. *The Selection of Essential Drugs (Technical Report Series 615)*. Geneva: World Health Organization, 1977.
21. World Health Organization. *The ICD Classification of Mental and Behavioral Disorder. Clinical Description and Diagnostic Guidelines*. Geneva: WHO, 1992.
22. World Health Organization . *Guidelines for ATC classification and DDD assignment*. 1st edition. WHO: Oslo, 1996.
23. WHO Collaborating Centre for Drug Statistic Methodology. *Guidelines for ATC classification and DDD assignment*. WHO: Oslo, 1998.
24. WHO Collaborating Centre for Drug Statistic Methodology. *Guidelines for ATC index with DDDs*. WHO: Oslo, 2002.
25. Yang SY, Kao Yang YH, Chong MY, Yang YH, Chang WH, Lai CS: Risk of extrapyramidal syndrome in schizophrenic patients treated with antipsychotics: A population-based study. *Clin Pharmacol Ther* 2006;81:586-94.

APPENDIX 1. Publications on REAP study

REAP-AP

(in English)

Chong MY, Tan CH, Fujii S, Yang SY, Ungvari G, Si T, Chung EK, Sim K, Shinfuku, N (2004). Antipsychotic drug prescription for Schizophrenia in East Asia: A rationale for change. *Psychiatry and Clinical Neurosciences* 58 (1), 61-67.

Sim K, Su A, Ungvari G, Fujii S, Yang SY, Chong MY, Si T, Chung EK, Tsang HY, Chan YH, Shinfuku N, Tan CH (2004). Depot antipsychotic use in schizophrenia: an East Asian perspective. *Human Psychopharmacology* 19 (1), 103-109.

Sim K, Su A, Fujii S, Yang SY, Chong MY, Ungvari GS, Si T, Chung EH, Tsang HY, Chan YH, Heckers S, Shinfuku N, Tan CH (2004). Antipsychotic polypharmacy in patients with schizophrenia: A multicentre comparative study in East Asia. *British Journal of Clinical Pharmacology* 58 (2), 178-183.

Sim K, Su A, Leong JY, Yip K, Chong MY, Fujii S, Yang SY, Ungvari GS, Si T, Chung EK, Tsang HY, Shinfuku N, Kua EH, Tan CH (2004). High dose antipsychotic use in schizophrenia: Research on East Asia Psychotropic Prescription (REAP) findings. *Pharmacopsychiatry* 37 (4), 175-179.

Yoshimura R, Okamoto T, Nakamura J, Tateno M, Otsuka K, Takahashi H, Fujisawa D, Takamatsu T, Fujii S, Sato S, Inoue M, Sasaki H, Kuroki T, Shinfuku N (2006). Prescription pattern of antipsychotic drugs for schizophrenic inpatients in Japan: Research on East Asia Psychotropic Prescription Pattern- Antipsychotics study. *Psychiatry and Clinical Neurosciences* 60 (6), 778-779.

(in Japanese)

Fujii S, Maeda K, Shinfuku N (2003). Survey on psychotropic drug prescription pattern in six countries and areas in East Asia. *Rinsyo seisin igaku* 32 (6), 629-646.

Fujii S, Shinfuku N (2004). The characteristics of pharmacotherapy for the inpatients with schizophrenia in Japan -Comparison with other countries and regions-. *Rinsyo seisin yakuri* 7 (1), 3-14.

Fujii S, Shinfuku N (2005). Utilization of levomepromazine in Japan – its role as an antipsychotic in psychiatric pharmacotherapy. *Rinsyo seisin yakuri* 8 (8), 1227-1238.

Fujii S, Tateno M, Otsuka K, Takahashi H, Fujisawa D, Takamatsu M, Sato S, Okamoto T, Yoshimura R, Inoue M, Sasaki H, Kuroki H, Shinfuku N (2005). Gaps in psychotropic prescription pattern between various areas in Japan. *Seishin iryo* 38, 17-25.

REAP-AD

(in English)

Sim K, Lee NB, Chua HC, Mahendran R, Fujii S, Yang SY, Chong MY, Si T, He YL, Lee MS, Sung KM, Chung EK, Chan YH, Shinfuku N, Tan CH, Sartorius N, Baldessarini RJ (2007). Newer antidepressant drug use in East Asian psychiatric treatment settings: REAP (Research on East Asia Psychotropic Prescriptions) Study. *British Journal of Clinical Pharmacology* 63 (4), 431-437.

Uchida N et al. (2007). An international study on prescription pattern of antidepressants at 20 teaching hospitals and major psychiatric institutions in East Asia; Analysis of 1,898 cases from China, Japan, Korea, Singapore and Taiwan. *Psychiatry and Clinical Neurosciences* 61(5): 522-528

(in Japanese)

Fujii S, Kaneko N, Kitsukawa H, Sasaki H, Nagai H, Ishii H, Nishimura R, Kuroki T, Nakamura J, Shirakawa O, Maeda K, Watanabe K, Nakagome K, Kanba S, Shinfuku N (2005). Trend of antidepressant usage in Japan: International collaborative prescription survey among 5 Asian countries and regions (REAP-AD). *JPN Bull Soc Psychiat* 14 (1), 30-35.

Tanaka M, Nagai H, Uchida N, Kawaguchi Y, Fujii S, Nishimura R, Tan CH, Shinfuku N (2007). The pattern of antidepressant usage in East Asia: International collaborative prescription survey among 5 Asian countries and regions (REAP-AD). *Jpn. J. Clin. Psychopharmacol.*, 10 (1), 131-146.

APPENDIX 2: List of National Collaborators and Technical Advisors

Project Coordinators:

Professor Shinfuku Naotaka (Japan)

Associate Professor Tan Chay Hoon (Singapore)

International Coordinators and Center Collaborators:

China:

Coordinators: Professor He Yang Lin (Shanghai)

Professor Si Tian-Mei (Beijing)

Collaborators:

Anding Hospital: Professor Ma Xin

Chengdu:

Hong Kong:

Coordinator: Professor Gabor Sandor Ungvari

Collaborators:

Assistant Professor Edwin Lee

Dr. Yu-Tao Xiang

India:

Coordinator: Professor Jintendra Trivedi (Lucknow)

Collaborators:

Professor Ajit Avasthi (Chnadigarh)

Professor Dipesh Bhagabati (Guwahati)

Professor Roy Abraham Kallivayalil (Kottayam)

Professor Shubhangi R. Parkar (Mumbai)

Dr. S.Haque Nizamie (Ranchi)

Professor Janardhan Reddy (Bangalore)

Japan:

Coordinator: Professor Shinfuku Naotaka (Fukuoka)

Collaborators:

Dr Santa Fujii (Kobe)

(Saga, Fukuoka, Okayama, Kobe, Tokyo and Sendai)

Korea:

Coordinator: Professor Sung Kil Min (Seoul)

Collaborators:

Singapore:

Coordinator: Professor Kua Ee Heok (Singapore)

Collaborators:

Dr Sim Kang

Dr Roger Ho Chun Man

Taiwan:

Coordinator: Professor Mian-Yoon Chong (Kaohsiung)

Collaborators:

Shu-yi Yang (Taipei)

Thailand:

Coordinator: Professor Pichet Udomratn (Songkhla)

Collaborators:

Dr. Apichai Mongkol (Bangkok)

Technical Advisers

Professor Norman Sartorius, Geneva (Overall Adviser)

Professor Mian-Yoon Chong, Kaohsiung (Epidemiology)

Ms Shu-yu Yang, Taipei (Pharmacology)

Associate professor Tan Chay Hoon, Singapore (Pharmacology)

Professor Tsutani Kiichiro, Tokyo (Pharmaco-economy)

Professor Wang Xiang Dong, Manila, (Liaison with WHO)

APPENDIX 3: Information on the collaborating site

Before entering into each patient's survey, please let us know the feature of your hospital

1. Name of hospital:

2. Name of the director:

3. Name of collaborator:

Address that we should use for correspondence with you:

Tel. _____ Fax _____ e-mail address _____

4. Type of your hospital:

a Psychiatric hospital General hospital University/Teaching general hospital

Other types

b Public (National Prefecture Others _____)

Private

5. Number of psychiatric beds : acute ward _____ beds, chronic ward _____ beds

6. Number of full time psychiatrists:

7. Number of other full time staff : _____ nurses, _____ psychiatric social workers

_____ occupational therapists, _____ psychologists

8. Percentage of inpatients with the diagnosis of schizophrenia : _____ %

9. Insurance : _____ % of patients covered by insurance (any kind)

10. Age distribution of the inpatients :

≤ 19 years old _____ patients (_____ %)

20–39 years old _____ patients (_____ %)

40–59 years old _____ patients (_____ %)

≥ 60 years old _____ patients (_____ %)

12. Sex distribution of the patients :

_____ male patients

_____ female patients

13. Duration of admission:

less than 1 year _____ patients (_____ %)

1 year – less than 5 years _____ patients (_____ %)

5 years—less than 10years _____ patients (_____ %)

10 years-less than 20 years _____ patients (_____ %)

more than 20 years _____ patients (_____ %)

13. Prescription policy (if you have some) :

a. No policy

b. Yes, we have a policy, as follows:

14. Other features of specific strengths of your hospital (please specify):

[Thank you very much for your collaboration.]

Data Form

< Inclusion Criterion >

Inpatients with diagnosis of schizophrenia on the day of survey will be included.

< Target Dates >

Oct 1 – 31, 2008

This form is to be completed by a physician in charge of the patient.

Date of Survey: Oct _____, 2008

Patient No : _____

Country: _____

Hospital: _____

Physician in charge: _____

Researcher: _____

Chart's (patient's record) number: _____

A) Profile of this patient

1. Age: ___ years
2. Weight: ___ kg; height: _____ cm
3. Sex: 1. M / 2. F
4. Date of the present admission (y/m/d): ___/___/
5. First admission: 1. Yes 2. No
6. Duration from the onset until now: _____ months
 1. Less than 3 months
 2. 3 months - Less than 6 months
 3. 6 months - Less than 1 year
 4. 1 year - Less than 5 years
 5. 5 years - Less than 10 years
 6. 10years - Less than 20 years
 7. More than 20 years

B) Diagnosis

7. Diagnosis of Schizophrenia was based on the following criteria (*please choose just 1 criterion*).
 1. ICD (coding No. _____)
 2. DSM (coding No. _____)
 3. National Criteria (e.g., CCMD)
 4. Other (_____)

C) Significant symptoms for the past 1 month

8. Significant symptoms for the past 1 month are, (*plural choice*)
 1. Delusions
 2. Hallucinations
 3. Disorganized speech, e.g. frequent derailment or incoherence
 4. Grossly disorganized or catatonic behavior
 5. Negative symptoms, e.g. affective flattening, alogia, or avolition
 6. Existence of social/occupational dysfunction
 - 7.1 Verbal aggression
 - 7.2 Physical aggression
 8. Other symptoms, e.g;

D) Course of illness for the past 1 year

9. Course of illness for the past 1 year is,

- 1. Continuing presence of symptoms
- 2. Variable course of illness
- 3. Long-term hospitalization (Applicable only for long stay for more than five years)

E) Prescription (all medications on the day of survey)

10. Depot injections 1. Yes 0. No

If yes, please write down as prescribed, any **depot injections given within past 1 month**

	Drug name/unit	doses	Frequency (q1w, or q2w or q1m)	Total dosage
e.g.	Fluanxol depot (flupentixol) 20mg/1ml/amp	1	q2w	20mg
	Binison depot (haloperidol) 50mg/1ml/amp			
	Clopixol depot (zuclopenthixol) 200mg/1ml/amp			
	Fluanxol depot (flupentixol) 20mg/1ml/amp			
	Flucan (fluphenazine) 25mg/1ml/amp			
	Haldol decanoas (haloperidol) 50mg/1ml/amp			
	U-dolan depot (haloperidol) 50mg/1ml/amp			

11. Other medication: 1. Yes 0. No

If yes, please write down as prescribed, other medication on the day of survey, within 24 hours, from 6am to 6am

	Drug name/unit	doses	Frequency (bid, qid, hs...)	Total dosage per day
e.g.	Haloperidol 2mg/tab	1	tid	6mg
e.g.	Trihexyphenidyl 2mg/tab	1	bid	4mg

F) ECT

12. Has this patient received ECT therapy within recent 1 month?

1. Yes 0. No

G) Adverse effects

13. Please tick the symptoms you observed in the particular patient *on the day of survey*.

[“9. No information” is the choice for item that requires patient’s complaint or laboratory data].

1) Movement disorders

	symptoms	<input type="checkbox"/> 1. Yes	<input type="checkbox"/> 0. No	<input type="checkbox"/> 9. No information
1	Rigidity			
2	Akinesia			
3	Tremor			
4	Akathisia			
5	Dystonia			
6	Tardive dyskinesia			
7	Others (<i>please specified</i>):			

2) Autonomic adverse effects

	symptoms	<input type="checkbox"/> 1. Yes	<input type="checkbox"/> 0. No	<input type="checkbox"/> 9. No information
1	Constipation			
2	Excessive salivation			
3	Dry mouth			
4	Postural hypotension			
5	Difficulty in micturition			
6	Blurring of vision			
7	Others (<i>please specified</i>):			

3) Endocrinological disturbance

	symptoms	<input type="checkbox"/> 1. Yes	<input type="checkbox"/> 0. No	<input type="checkbox"/> 9. No information
1	Sexual dysfunction			
2	Galactorrhea, amenorrhea in women or gynecomastia in men			
3	Others (<i>please specified</i>):			

4) Metabolic dysfunction (*within the past 3 months*)

	symptoms	<input type="checkbox"/> 1. Yes	<input type="checkbox"/> 0. No	<input type="checkbox"/> 9. No information
1	Impaired glucose tolerance (hyperglycaemia, diabetes mellitus, diabetic ketoacidosis)			
2	Hypercholesterolemia			
3	Weight gain <i>If yes, from baseline from ____ kg to ____ kg</i>			
4	Others (<i>please specified</i>):			

5) Cardiovascular adverse effects (*within the past 3 months*)

	symptoms	<input type="checkbox"/> 1. Yes	<input type="checkbox"/> 0. No	<input type="checkbox"/> 9. No information
1	QTc-interval lengthening ($QTc > 456 \text{ ms}$)			

6) Others

	symptoms	<input type="checkbox"/> 1. Yes	<input type="checkbox"/> 0. No	<input type="checkbox"/> 9. No information
1	Over sedation (drowsy most of day)			
2	Others (<i>please specified</i>):			

Thank you very much for your kind collaboration.

APPENDIX 5:
INFORMED CONSENT

Patient name: _____

Date of Birth: _____

I agree to participate in the research for the assessment of antipsychotics use in Asia (REAP-AP3). About 100 patients will be enrolled from each center. I am diagnosed with schizophrenia and the purpose of the study is to evaluate schizophrenia symptoms and the treatment undertaken through interview.

Study Procedure

I will be interviewed by a psychiatrist, and a clinical history and psychiatric examination will be conducted.

Risks and discomforts

The procedure that will be undertaken is not invasive and has negligible risks.

Confidentiality

The ethical committee of the hospital has approved the study, and the information contained in this study will be carefully stored and protected against release to unauthorized people.

Patient Declaration

I have voluntarily accepted to participate in this study.

Through the investigator's explanation of the purpose of the study and this declaration of informed consent described, all of my queries were resolved.

Patient signature: _____

Date _____

Witness signature: _____

Date _____

Investigator signature: _____

Date _____