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Clozapine prescription pattern in patients with schizophrenia in Asia: The REAP survey (2016)

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ABSTRACT

Clozapine is an effective antipsychotic medication for treatment resistant schizophrenia and is widely used in Asian countries. This study investigated clozapine prescription patterns and their associated factors in Asian countries and territories based on the database of the Research on Asian Psychotropic prescription study (REAP) conducted in 2016. Demographic and clinical information of 3744 schizophrenia patients in 15 Asian countries and territories was collected with a standardized data collection form. In total, 18.4% of the sample received clozapine, ranging from 2.6% in Japan to 32.3% in Hong Kong. Binary logistic regression analysis revealed that higher antipsychotic dose (OR = 1.002, $P < 0.001$), less frequent first admission in the sample (OR = 0.6, $P < 0.001$), more severe negative symptoms (OR = 1.4, $P = 0.001$) and less first generation antipsychotics (FGAs) (OR = 0.2, $P < 0.001$) were independently and significantly associated with clozapine prescription. Clozapine is frequently and increasingly prescribed for schizophrenia in Asia, with large variation across countries and territories. Given the diverse prescription patterns of clozapine found in Asian countries/territories, the clinical rationale of clozapine prescription needs careful consideration in Asia with more local input.

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1. Introduction

Schizophrenia is a chronic and debilitating psychiatric condition with prevalence between 0.5%–1% worldwide. Up to one third of schizophrenia patients have inadequate or partial response to two or more antipsychotics from different classes (Simeone et al., 2015; Siskind et al., 2018).

Clozapine was introduced to clinical practice around 50 years ago first as a mainstream antipsychotic drug and from Kane et al.'s (Kane et al., 1988) landmark study more specifically for treatment-resistant schizophrenia (TRS). Clozapine is the only antipsychotic medication approved for TRS in many countries (Taylor et al., 2000). Due to fatalities from agranulocytosis reported in Finland in 1974, clozapine was withdrawn from the market in many Western countries but it was later approved again in the US and all over the Western world because of its unique efficacy, and the introduction of complex safety measures designed to reduce the risk of agranulocytosis (Crilly, 2007). Compared to all other antipsychotics, clozapine is most efficacious in TRS (Barber et al., 2017). Clozapine reduces the risk of hospitalization, improves psychosocial functioning and overall quality of life, decreases extrapyramidal side effects and all-cause mortality (Chakos et al., 2001; Tiihonen et al., 2017; Olagunju et al., 2018; Vermeulen et al., 2018). In addition, clozapine could also improve treatment-refractory mood disorders (Ranjan and Meltzer, 1996), lower the risk of recurrences of psychotic bipolar disorder, reduce total inpatient days and the number of emergency room visits (Wu et al., 2015), as well as reduce psychiatric admissions and inpatient days in borderline personality disorder (Rohde et al., 2017).

There is increasing evidence that the brain glutamate system is involved in the pathophysiology of schizophrenia (Kantrowitz and Javitt, 2012). Clozapine increases GABA-B receptor-mediated inhibitory neurotransmission (Daskalakis and George, 2009; Zink and Correll, 2015). Clozapine is not recommended as first-line treatment due to a range of adverse events (agranulocytosis, sedation, hypotension, and risk of myocarditis and metabolic syndrome, among others), which leads to poor treatment adherence as well as underutilization of clozapine (De Berardis et al., 2018; Li et al., 2018). Regular surveys are useful to rationalize prescription patterns of psychotropic medications (Sim et al., 2011; Wang et al., 2016; Xiang et al., 2017). Findings on clozapine prescription patterns varied considerably probably due to clinicians' and patients' attitudes towards its advantage and adverse events; for instance, the proportion of clozapine prescription in TRS was 33.3% in Australia and 54% in the UK, while the figures in schizophrenia ranged between 13.7% and 18.6% in Spain (Kar et al., 2016; Sanz-Fuentenebro et al., 2018). In Asian countries, the prescription pattern of clozapine ranged between 14.5% and 15.9% in schizophrenia inpatients (Xiang et al., 2011).

The objective of this study was to examine clozapine prescription patterns for schizophrenia and their associated factors in Asia.

2. Methods

2.1. Study settings and patients

The Research on Asian Psychotropic Prescription study (REAP) is an international psychopharmaco-epidemiological, cross-sectional survey on prescription patterns of psychotropic medications conducted by a group of psychiatrists, pharmacologists, and epidemiologists in Asia. The first REAP survey (REAP-AP1) was conducted in July 2001 involving 2399 schizophrenia patients in 31 hospitals, followed by REAP-AP2 in July 2004 with 2136 patients in 25 hospitals, and REAP-AP3 in October 2008-March 2009 with 2226 patients in 50 hospitals. The findings of the first three REAP surveys have been reported previously (Xiang et al., 2011, 2013). The REAP-AP4 survey was carried out in March–May 2016; 3744 schizophrenia patients were enrolled in 71 hospitals in 15 countries/territories including mainland China (China thereafter), Hong Kong, Thailand, Malaysia, Bangladesh, Japan, Taiwan, India, Indonesia, Myanmar, Pakistan, Korea, Singapore, Sri Lanka and Vietnam.

A consensus meeting was held prior to the survey and the method of data collection was discussed. Patients diagnosed with schizophrenia according to the ICD or DSM systems in the participating hospitals during the pre-defined study period were included in the survey. In most Asian countries/territories, psychiatric patients with severe medical conditions are rarely treated in psychiatric hospitals, therefore patients with major medical conditions requiring ongoing treatment by specialists were excluded from the survey in case were accidentally admitted to the hospitals participating in the survey. Antipsychotic doses were converted into chlorpromazine equivalent milligrams (CPZeq) (APA, 1997; Kane et al., 1998; Woods, 2003).

The protocol of the survey was evaluated and approved by the Research Ethics Committee of all participating hospitals. Informed consent was waived at some study sites if the data were collected only by a review of medical records according to local ethics regulation (Shinfuku and Tan, 2008). Informed consent were provided by patients who were interviewed.

2.2. Data collection

Following previous REAP surveys (Xiang et al., 2011; Xiang et al., 2013), basic socio-demographic and clinical data were collected by either a review of medical records or an interview using a data collection sheet designed for the REAP surveys. Type and dose of antipsychotic, antidepressants, mood stabilizers, anticholinergic drugs and benzodiazepine medications prescribed on a census day and the presence/absence of positive (delusions or hallucinations) and negative symptoms (affective flattening, alogia or avolition) in the past month, weight gain, extrapyramidal symptoms (rigidity, akinesia, tremor, akathisia, dystonia and tardive dyskinesia in the past three months were recorded. Due to the different treatment options, tardive dyskinesia is analyzed separately from other forms of extrapyramidal symptoms. For logistical reasons, treatment adherence could not be monitored. The abovementioned data were collected by research team members of the REAP project after obtaining the permission from the patients' treating psychiatrists.

2.3. Statistical analysis

Data were analyzed with the SPSS software, Version 21.0 for Windows. Continuous and categorical variables were described as means with standard deviations and frequencies with percentages, respectively. Univariate analyses including chi-square tests, independent samples t-tests, and Mann-Whitney U tests were conducted to compare the demographic and clinical data between clozapine and other antipsychotic groups. Binary logistic regression analysis was performed to determine the correlates of clozapine prescription, with clozapine as the dependent variable, while variables that significantly differed in the univariate analyses were entered as independent variables. The level of significance was set at 0.05, with two-sided test.

3. Results

Socio-demographic and clinical data and information on psychotropic medications are shown in Table 1. The majority of patients (n = 2200; 58.8%) were males. In the whole sample, 18.4% of patients received clozapine, with the highest proportion in Hong Kong (32.3%) and the lowest in Japan (2.6%) (Fig. 1).

The comparisons of the demographic and clinical data between the clozapine and non-clozapine groups are shown in Table 2. Patients on clozapine were more likely to have higher daily antipsychotic doses, more frequent negative symptoms and weight gain, but were less likely to be admitted for the first time and receive first-generation

Table 1
Socio-demographic and clinical characteristics and psychotropic drug prescription.

	China 2016	Hong Kong 2016	Japan 2016	Korea 2016	Singapore 2016	Taiwan 2016	India 2016	Thailand 2016	Malaysia 2016	Bangladesh 2016	Indonesia 2016	Myanmar 2016	Pakistan 2016	Sri Lanka 2016	Vietnam 2016	Total 2016
Patients (n)	160	31	229	131	171	403	479	322	305	99	581	164	298	97	274	3744
Age (year)																
Mean	39.7	38.8	46.5	40.5	48.1	47.6	36.0	39.3	39.3	31.9	34.9	37.6	36.9	40.4	38.7	39.5
SD	16.4	13.9	14.4	12.5	13.7	11.7	11.7	12.3	12.3	11.0	11.3	11.2	11.9	13.3	12.0	13.1
CPZeq (mg/day)																
Mean	552	470	668	584	397	430	387	327	303	593	287	280	523	434	550	421
SD	339	285	597	588	349	377	332	245	287	391	217	124	447	421	338	375
Clozapine dose (mg/day)																
Mean	250	295	404	423	411	218	248	141	264	142	58	193	185	368	182	198
SD	118	149	121	129	144	170	173	92	159	63	74	125	253	145	75	167
Male (%)	65.0	58.1	61.1	45.0	37.4	45.2	66.6	65.8	51.5	58.6	63.7	65.2	56.4	59.8	67.2	58.8
First admission (%)	35.6	9.7	7.9	1.5	8.8	4.2	18.0	14.3	7.9	30.3	23.4	23.2	11.1	17.5	33.9	16.4
Positive symptoms (%)	47.5	45.2	68.1	31.3	65.5	60.0	58.7	42.2	54.4	98.0	57.1	75.0	86.6	46.4	79.9	61.4
Negative symptoms (%)	61.9	64.5	64.6	31.3	48.0	51.4	48.4	3.7	32.8	64.6	29.3	58.5	64.1	33.0	72.3	45.2
Extrapyramidal symptoms (%)	16.3	25.8	45.9	19.8	46.2	38.5	44.5	20.8	16.7	36.4	14.6	19.5	42.3	26.8	47.1	31.1
Tardive dyskinesia (%)	0.0	0.0	2.2	0.0	4.1	5.0	1.3	0.3	3.0	0.0	0.3	0.6	2.3	0.0	1.5	1.7
Weight gain (%)	27.5	9.7	5.7	4.6	9.9	3.5	18.6	13.7	17.7	2.0	9.5	20.1	9.7	3.1	13.5	11.8
Use of FGA (%)	29.4	3.2	32.3	17.6	19.3	25.1	18.8	58.7	21.6	31.3	36.5	17.1	32.6	18.6	54.4	31.0
Use of non-clozapine SGA (%)	65.0	67.7	86.0	80.2	73.7	58.6	59.7	25.8	64.3	80.8	56.8	86.6	70.5	62.9	59.1	62.5
Use of clozapine (%)	31.9	32.3	2.6	10.6	12.3	25.0	24.2	29.8	9.5	3.0	22.9	4.3	11.0	20.6	18.6	18.4
Use of clozapine + other antipsychotics	23.1	6.5	0	3.1	7.0	10.2	6.7	17.1	3.3	3.0	20.0	0.6	7.0	14.4	11.7	10.1

CPZeq, chlorpromazine equivalents; FGA, first-generation antipsychotics; SGA, second-generation antipsychotics. Study sites in India, Thailand and Malaysia joined the survey in 2009, study sites in Bangladesh, Indonesia, Myanmar, Pakistan, Sri Lanka and Vietnam joined the survey in 2016.

antipsychotics (FGAs). In multivariate analysis, higher antipsychotic dose, less frequent first admission and FGAs, and more severe negative symptoms were independently and significantly associated with clozapine prescription (Table 3). Table 4 shows the indications of clozapine in different Asian countries and territories.

4. Discussion

Because of its side effects profile, particularly agranulocytosis, cardiovascular effects and metabolic syndrome, treatment with clozapine requires extra caution and heightened attention to treatment adherence (Young et al., 1998; Iqbal et al., 2003; Mustafa et al., 2015). Because of its superior efficacy, clozapine is recommended as a first choice for TRS (Warnez and Alessi-Severini, 2014; Stepnicki et al., 2018).

Clozapine prescription in schizophrenia in Asia increased from 14.5%-15.9% in the first three REAP surveys to 18.4% by 2016, with an ascending trend in most participating countries and territories. However, considering that up to a third of schizophrenia patients are treatment-resistant (Simeone et al., 2015; Siskind et al., 2018), the increase still represent under-prescription of clozapine in some countries (Warnez and Alessi-Severini, 2014). The requirement of mandatory blood testing and concerns about serious adverse events may be major barriers for clozapine use (Farooq et al., 2018). Due to insufficient health budget and lack of blood monitoring systems, clozapine prescription are restricted in some developing countries (Phanthunane et al., 2011; Farooq et al., 2018).

Many factors impacted on the variation of clozapine prescription rates across the participating countries/territories, such as resources of the health system, costs of clozapine and other antipsychotics, clinical traditions and regulations, access to other antipsychotics, and genetically determined inter-ethnic differences (Xiang et al., 2011; Bachmann et al., 2017; Farooq et al., 2018). For instance, in China treatment guidelines stipulates that clozapine could be prescribed only if FGAs and other second-generation antipsychotics (SGAs) are not effective after 6–8 weeks of treatment. In addition, mandatory blood monitoring needs to be carried out weekly or biweekly in the first 6 months of treatment and subsequently at least monthly (Chinese Medical Association, 2003). In contrast, in Japan, the regulation for clozapine initiation is even stricter, mandating hospitalization for at least 18 weeks and weekly hematological tests for the first 26 weeks. These and other logistically demanding requirements could partly account for the very low prescription rate of clozapine use (Bachmann et al., 2017; Verdoux et al., 2018). Clinicians' experience with clozapine and patients' attitudes towards blood monitoring and side-effects could also affect clozapine prescription (Bachmann et al., 2017).

Clozapine prescription was independently associated with a number of demographic and clinical factors. Clozapine is mainly prescribed for patients with TRS (Stepnicki et al., 2018), which explains the low rate of clozapine in first admission patients. Negative symptoms that are common in TRS are less likely to respond to other antipsychotics, therefore TRS patients are more likely to receive clozapine (Chakos et al., 2001). In this survey, adjunctive FGAs were less likely prescribed with clozapine probably due to the lack of evidence

Table 2
Comparison of the clozapine and non-clozapine groups with regard to socio-demographic and clinical characteristics (n = 3744).

	Clozapine (n = 691)		Non-clozapine (n = 3053)		Statistics		
	Mean	SD	Mean	SD	Z	df	P value
Age (year)	39.5	12.1	39.5	13.4	0.5†	–	0.6
Antipsychotic dose (CPZeq mg/day)	540	353	394	375	13.1†	–	**<0.001**
	N	**%**	**N**	**%**	**x^2**	**df**	**P value**
Male patients	418	60.5	1782	58.4	1	1	0.3
First admission	85	12.3	530	17.4	10.5	1	**0.001**
Positive symptoms	414	59.9	1884	61.7	0.8	1	0.4
Negative symptoms	339	49.1	1353	44.3	5.1	1	**0.02**
EPS	195	28.2	969	31.7	3.3	1	0.07
Tardive dyskinesia	7	1	55	1.8	2.2	1	0.1
Weight gain	101	14.6	342	11.2	6.3	1	**0.01**
Prescription of FGA	133	19.2	1026	33.6	54.4	1	**<0.001**
Prescripion of non-clozapine SGA	247	35.7	2339	76.6	1410.7	1	**<0.001**

EPS, extrapyramidal side effects; CPZeq, chlorpromazine equivalents; FGA, first-generation antipsychotics; SGA, second-generation antipsychotics; †Mann-Whitney U test; bold p-values ≤0.05.

Table 3
Factors associated with clozapine use: multiple logistic regression analysis with the non-clozapine cohort as the reference group (n = 3744).

	P	Odds ratio	95%CI
Age (year)	0.4	1.003	0.995–1.01
Antipsychotic dose (CPZeq mg/day)	**<0.001**	1.002	1.002–1.002
Male sex	0.8	1.03	0.9–1.2
First admission	**<0.001**	0.6	0.5–0.8
Positive symptoms	0.3	1.1	0.9–1.4
Negative symptoms	**0.001**	1.4	1.1–1.7
Acute extrapyramidal symptoms	0.07	0.8	0.7–1.02
Tardive dyskinesia	0.3	0.7	0.3–1.5
Weight gain	0.06	1.3	0.99–1.7
Prescription of FGA	**<0.001**	0.2	0.2–0.3

CPZeq = chlorpromazine equivalents; FGA = first-generation antipsychotics; study sites have been controlled for as a covariate; bold p-values ≤0.05.

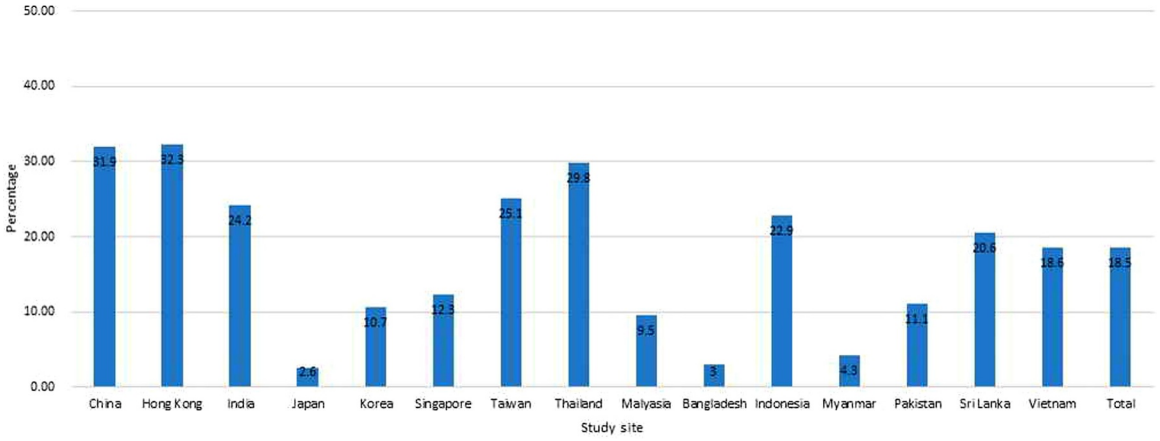

Fig. 1. Use of clozapine by country and territories.

Table 4
Indications of clozapine in selected Asian countries and territories.

	Indications for clozapine
China	1) Treatment-resistant schizophrenia; 2) Schizophrenia patients with severe tardive dyskinesia; 3) Patients with a low threshold for occurrence of extrapyramidal adverse reactions; 4) Schizoaffective disorder, refractory mania and severe psychotic depression; 5) Psychotic symptoms secondary to anti-Parkinson's drugs; 6) Schizophrenia patients with severe suicidality; 7) Other refractory psychiatric disorders, such as extensive developmental disorders, autism or obsessive-compulsive disorder.
Hong Kong	Treatment-resistant schizophrenia and schizoaffective disorder.
Japan	Treatment-resistant schizophrenia
Korea	1) Patients with treatment-resistant schizophrenia 2) Schizophrenia patients who do not adequately respond to both first- and second-line antipsychotics 3) Schizophrenia patients with severe extrapyramidal symptoms (especially tardive dyskinesia) 4) Schizophrenia or schizoaffective disorder patients with the risk of suicidal behaviors
Singapore	1) Treatment resistant schizophrenia 2) Schizophrenia spectrum conditions with intolerable extrapyramidal symptoms when other all non-clozapine antipsychotics have been tried with inadequate benefit
Taiwan	1) Treatment resistant schizophrenia; 2) Reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorders; 3) Drug induced psychosis in Parkinson's disease.
India	1) Treatment-resistant schizophrenia; 2) Schizophrenia patients with severe tardive dyskinesia; 3) Patients with a low threshold for occurrence of extrapyramidal adverse reactions;
Malaysia	1) Treatment resistant schizophrenia 2) Schizophrenia with persistent positive symptoms for more than 2 years 3) Schizophrenia with recurrent suicidal idea 4) Schizophrenia with recurrent aggressive behaviour
Bangladesh	1) Treatment resistant schizophrenia 2) Schizophrenia patients with sucidal ideation and attempts 3) Psychotic patients with tardive dyskinesia 4) Schizophrenia patients with affective symptoms (i.e.,manic symptoms)
Indonesia	1) Treatment-resistant schizophrenia 2) Treatment of schizoaffective disorder 3) Treatment-resistant bipolar disorder 4) Treatment for agitated or aggressive patients 5) Treatment for patients on antipschotic agents with persistent extrapyramidal syndrome 6) Treatment for Schizophrenic patients with severe suicidal ideas and/or attempts
Myanmar	1) Treatment-resistant schizophrenia 2) Schizophrenia patients with tardive dyskinesia 3) Schizophrenia patients with high sensitivity to extrapyramidal side effects
Pakistan	1) Treatment-resistant schizophrenia; 2) Schizoaffective disorder, refractory mania and severe psychotic depression; 3) Schizophrenia patients with severe suicidality;

supporting the effectiveness of such combinations and the higher possibility of EPS (Correll et al., 2004; Siskind et al., 2018). The association between clozapine and weight gain is well-established (De Berardis et al., 2018), although their association did not reach significance level in this study. Higher antipsychotic dose prescribed to patients receiving clozapine is probably explained by the higher percentage of TRS in the clozapine group, who needs higher doses (Lindenmayer et al., 2011). It should be noted that converting antipsychotic doses into chlorpromazine equivalents, particularly for SGAs, is a crude approximation made on clinical grounds and not by objective measures like a PET scan.

The strengths of this survey included the large sample size and more extensive coverage of Asia than previous REAP surveys. Limitations of the survey should also be acknowledged. First, the survey sites were not randomly selected, although patients were consecutively screened and enrolled. Moreover, patients with significant physical comorbidities were excluded. Therefore, the findings could not be generalized to all schizophrenia patients in Asia. Second, due to logistical reasons, potentially important variables associated with clozapine prescription, such as pre-existing psychiatric diagnoses, history of psychotropic treatment, patients' socio-economic background, local prescription guidelines and reimbursement policies, were not recorded. Standardized rating scales measuring psychopathology, side effects of antipsychotics and rigorous assessment of physical comorbidities were not used, but they should be employed in future studies. Third, owing to the cross-sectional design, the causality between clozapine prescription and demographic and clinical variables, as well as changes of clozapine prescription over time, could not be examined. The appropriateness of clozapine prescriptions also needs to be examined in prospective studies.

In conclusion, compared to previously reported figures from the Asian continent, clozapine prescription for Asian schizophrenia patients has increased over time, with considerable variations across countries and territories. The clinical rationale of clozapine prescription needs careful consideration in Asia.

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Disclosure statement

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