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Patterns of long acting injectable antipsychotic use and associated clinical factors in schizophrenia among 15 Asian countries and region

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Abstract

Introduction: Patterns of clinical use of long-acting injectable (LAI) antipsychotic drugs in many countries, especially in Asia, for treatment of patients diagnosed with chronic psychotic disorders including schizophrenia are not well established.

Methods: Within an extensive research consortium, we evaluated prescription rates for first- (FGA) and second-generation antipsychotic (SGA) LAI drugs and their clinical correlates among 3557 subjects diagnosed with schizophrenia across 15 Asian countries and region.

Results: Overall, an average of 17.9% (638/3557; range: 0.0%-44.9%) of treated subjects were prescribed LAI antipsychotics. Those given LAI vs orally administered agents were significantly older, had multiple hospitalizations, received multiple antipsychotics more often, at 32.4% higher doses, were more likely to manifest disorganized behavior or aggression, had somewhat superior psychosocial functioning and less negative symptoms, but were more likely to be hospitalized, with higher BMI, and more tremor. Being prescribed an FGA vs SGA LAI agent was associated with male sex, aggression, disorganization, hospitalization, multiple antipsychotics, higher doses, with similar risks of adverse neurological or metabolic effects. Rates of use of LAI antipsychotic drugs to treat patients diagnosed with schizophrenia varied by more than 40-fold among Asian countries and given to an average of 17.9% of treated schizophrenia patients. We identified the differences in the clinical profiles and treatment characteristics of patients who were receiving FGA-LAI and SGA-LAI medications.

Discussion: These findings behoove clinicians to be mindful when evaluating patients' need to be on LAI antipsychotics amidst multifaceted considerations, especially downstream adverse events such as metabolic and extrapyramidal side effects.

KEYWORDS
antipsychotic drugs, long-acting injectable, schizophrenia

1 | INTRODUCTION

Unreliable adherence to prescribed treatment is a major source of limited effectiveness of treatment in general, and is of particular concern for patients with schizophrenia and other severe, chronic psychiatric disorders (García, Martínez-Cengotitabengoa, & López-Zurbano, 2016; Sendt, Tracy, & Bhattacharyya, 2015) Several large clinical studies have documented low levels of long-term treatment adherence among patients diagnosed with schizophrenia. For example, the US Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study found that 74% of subjects discontinued oral antipsychotic medication within 18 months (Czobor, Van Dorn, & Citrome, 2015; Lieberman et al., 2005). Potential consequences of such treatment nonadherence include markedly increased risks of clinical worsening and hospitalization, and potential risk of suicide (Higashi et al., 2013). There has been hope that use of long-acting injectable (LAI) or depot preparations of antipsychotic medications would increase long-term-treatment-adherence and enhance the effectiveness of treatment. Such agents started with esters of fluphenazine and haloperidol in the 1960s and 1970s, followed by additional esters as well as agents made long-acting by other pharmacological mechanisms (Baldessarini, 2013; Haddad, Brain, & Scott, 2014; Jann & Penzak, 2018; Johnson, 2009). There was a resurgence of interest in LAI antipsychotics after the launch of risperidone in a LAI form based on its incorporation into slowly hydrolyzed carbohydrate microspheres (Sampson, Hosalli, Furado, & Davis, 2016). This was the first second-generation depot antipsychotic developed, with similar preparations involving other atypical antipsychotics, including aripiprazole,

olanzapine, and paliperidone (Baldessarini, 2013; Jann & Penzak, 2018; Rauch & Fleischhacker, 2013). Studies of long-acting-second-generation antipsychotics (SGAs) have shown consistent superiority to placebo regarding relapse prevention and symptom reduction in schizophrenia, as would be expected of clinically employed treatments with regulatory approval (Keating et al., 2017; Rauch & Fleischhacker, 2013; Titus-Lay, Ansara, Isaacs, & Ott, 2018). However, anticipated superiority of LAI vs orally administered antipsychotic drug treatment has been found only in some trials—more often in nonrandomized or retrospective trials, whereas prospective, randomized trials have not consistently yielded significant differences between oral and LAI treatments (Buckley, Schooler, & Goff, 2015; Kirson et al., 2013; Kishimoto et al., 2018).

Reported benefits of treatment with LAI antipsychotics include lower overall treatment costs, associated in large part with reduction of costs of hospitalization (Marcus & Olfson, 2008). Clinical benefits include reduced rates of refusal or discontinuation of treatment, with more reliable delivery of active drug over time—all of which can contribute to reduced risk of exacerbations of illness (Brissos, Veguilla, & Taylor, 2014; Siegel, 2005; Subotnik et al., 2015). Treatment involving injectable antipsychotic drugs can provoke concerns about perceived intrusiveness and coercion (Patel, de Zoysa, Bernadt, Bindman, & David, 2010) and such concerns can differ with cultural and other sociological factors. Often they can be resolved successfully by greater efforts to discuss pros and cons with patients and to involve them more actively in treatment decisions (Brissos et al., 2014; Patel et al., 2010). Physical discomfort and pain at the injection site also are potential problems of LAI antipsychotics (Bloch, Mendlovic, & Strupinsky, 2001).

In general, the numbers of well-designed, controlled, and randomized treatment trials comparing orally administered with LAI antipsychotics are relatively few, and comparisons of LAI preparations of FGA and SGA agents remain inadequate (Jann & Penzak, 2018). Additionally, comparisons of such preparations given at different intervals (from weekly to quarterly) are rare (Carr, Hall, & Roche-Desilets, 2016). Moreover, information about current acceptance of LAI antipsychotics in various Asian cultures is very limited. Reported rates of use of LAI antipsychotic agents in Western countries suggest wide regional differences, with usage rates ranging from 8% to 35% among patients with schizophrenia (Barnes, Shingleton-Smith, & Paton, 2009; Potkin, Bera, Zubek, & Lau, 2013; Sneider, Pristed, Correll, & Nielsen, 2015). Our earlier survey, conducted more than a decade ago in six Asian countries found an average usage rate of 15.3%, with a preference for older, FGA LAI agents (Sim et al., 2004).

The preceding observations encouraged the present study of a large sample of patients diagnosed with schizophrenia in 15 Asian countries and region, to determine the rates of use of LAI preparations of both FGAs and SGAs in comparison to the use of orally administered antipsychotic agents. We also sought to identify geographic and clinical factors that were associated with rates of LAI usage. Based largely on informal clinical observations, we hypothesized that LAI antipsychotic drug use is becoming more prevalent in some Asian regions, and that LAI preparations of both FGA and SGA agents are being used.

2 | METHODS

2.1 | Study sample and procedures

We evaluated data collected in 2016 from 3577 subjects with schizophrenia in the Research on Asian Psychotropic prescription patterns in Schizophrenia (REAP-SZ) project, a pharmaco-epidemiological study initiated in 1999 (Chong, Tan, & Fujii, 2004). Data collected include details of usage of both FGA and SGA LAI antipsychotics for patients diagnosed with schizophrenia across 15 Asian countries and region (Bangladesh, Hong Kong SAR, India, Indonesia, Japan, Malaysia, Myanmar, Pakistan, PR China, RO Korea, Singapore, Sri Lanka, Taiwan, Thailand, and Vietnam). Data collection followed the same protocol at each site. We recruited consecutive subjects diagnosed with schizophrenia by standard international criteria and receiving antipsychotic drug treatment in various ambulatory and inpatient settings. Data recorded included current age, sex, diagnosis, duration of illness, setting of treatment (outpatient or inpatient), selected clinical features, all medicines and doses prescribed by clinicians responsible for care of the subjects. Diagnoses were confirmed at each site by experienced project investigators, following ICD-10(World Health Organization [WHO], 1992) or Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. The study protocol was approved by an Institutional Review Board at each collaborating site. All participants were fully informed of the aims of the study and provided written, informed consent for anonymous and aggregate reporting of their findings. Depot intramuscular injections of antipsychotics and their doses within 30 days of admission were recorded. Daily doses of antipsychotics, including LAI antipsychotics, were converted to approximate chlorpromazine equivalents (CPZ-eq mg/day) using guidelines as described previously (Baldessarini, 2013; Gardner, Murphy, O'Donnell, Centorrino, & Baldessarini, 2010; Kane et al., 1998).

2.2 | Data analyses

Statistical analyses are based on the Statistical Package for the Social Sciences (SPSS) (IBM Corp, 2015). Averages are reported as means ±SD or 95% confidence intervals (CI), and rates (%) as well as Odds Ratios (OR) are reported with confidence intervals (CIs). Normality of distributions of continuous measures was tested with the Kolmogorov-Smirnovone-sample test before further analysis. Differences between subjects receiving a LAI antipsychotic or not were tested by ANOVA (*t*-test) for normally distributed continuous data and nonparametric Mann-Whitney*U* tests for nonnormally distributed continuous data; contingency tables (χ^2) were used for categorical variables. Multivariate logistic regression modeling was used to test for influences of adjust for relevant covariates and to determine factors associated significantly and independently with LAI vs oral

TABLE 1 Characteristics of 15 samples of Asian schizophrenia patients treated with long-acting injected (LAI) or oral antipsychotics

Country	Subjects	Age (years)	Males (%)	Hospitalized (%)	First admission (%)	In remission (%)	LAI usage (%)	LAI use or [CI]	LAI CPZ-eq (mg/day)	Total CPZ-eq (mg/day)
Bangladesh	50	33.4 ± 10.1	58.0	0.00	-	30.0	16.0	2.91 [1.08-7.85]	219 ± 57.9	580 ± 221
PR China	152	40.9 ± 16.0	65.1	90.8	36.2	48.7	0.66	0.01 [0.01-0.80]	375 ± 10.1	507 ± 277
Hong Kong	31	38.8 ± 13.9	58.1	100.0	9.70	71.0	6.50	1.06 [0.22-5.07]	219 ± 133	391 ± 213
India	475	36.0 ± 11.7	66.5	31.2	55.6	65.7	15.8	2.87 [1.45-5.69]	229 ± 99.9	396 ± 293
Indonesia	539	36.2 ± 10.4	64.0	50.5	45.6	59.7	8.30	1.39 [0.69-2.83]	216 ± 172	333 ± 211
Japan	219	46.6 ± 14.3	62.1	58.4	14.1	35.2	8.20	1.38 [0.62-3.07]	285 ± 91.6	530 ± 491
RO Korea	112	39.3 ± 12.1	44.6	5.40	33.3	42.0	13.4	2.37 [1.02-5.48]	425 ± 193	534 ± 470
Malaysia	292	39.2 ± 12.1	51.7	34.2	24.0	66.8	44.9	12.4 [6.21-24.6]	188 ± 122	345 ± 269
Myanmar	163	37.7 ± 11.2	65.6	55.2	42.2	37.4	6.10	1.00	138 ± 44.5	325 ± 112
Pakistan	287	37.2 ± 11.9	55.1	47.7	20.4	36.9	23.0	4.57 [2.28-9.17]	155 ± 103	647 ± 663
Singapore	160	47.9 ± 13.5	35.6	73.1	11.1	24.4	43.8	11.9 [5.84-24.2]	163 ± 103	397 ± 272
Sri Lanka	96	40.6 ± 13.1	60.4	52.1	34.0	30.2	38.5	9.60 [4.49-20.5]	199 ± 95.3	499 ± 424
Taiwan	392	47.5 ± 11.8	45.7	56.6	7.20	52.6	16.6	3.04 [1.52-6.08]	189 ± 116	341 ± 271
Thailand	319	39.4 ± 12.3	66.5	42.9	32.1	60.2	29.8	6.49 [3.28-12.8]	237 ± 125	414 ± 308
Vietnam	270	39.1 ± 11.7	67.4	100.0	33.3	16.7	0.00	-	-	531 ± 336
Totals [95%CI]	3557	39.9 [37.8-47.0]	57.8 [52.5-63.1]	53.2 [36.8-69.7]	28.5 [20.4-36.6]	45.2 [35.8-54.5]	17.9 [9.69-26.0]	-	231 [184-278]	451 [395-507]

Note: Data are means ± SD, or OR [with 95%CI]. OR for LAI usage compares with Myanmar as the reference country (OR = 1.00); all OR differ significantly from the null of 1.00, except for Hong Kong, Indonesia, and Japan. Note that usage rates of LAI antipsychotics are highest in Malaysia (44.9% of schizophrenia patients), Singapore (43.8%), and Sri Lanka (38.5%), and lowest in Vietnam (0.00%) and PR China (0.70%). CPZ-eq mg/day doses of LAI drugs and total doses of all antipsychotics are not significantly associated with the rate of use of LAI antipsychotics (r = 0.412 and 0.139; both $P \geq .14$), nor are total daily doses and doses of LAI agents correlated (r = 0.345, P = .23).

antipsychotic treatment or differences between subjects given LAI FGA vs SGA agents. Statistical significance was set at $P < .05$.

3 | RESULTS

Of the 3577 subjects included, mean current age was 39.9 [CI: 37.8-47.0] years (Table 1, Figure 1). The majority of subjects were male (57.8%) and currently hospitalized (53.2%). Usage of LAI antipsychotics in the 3577 subjects averaged about 17.9% [CI: 9.69-26.0], with wide international variations, ranging from 0% in Vietnam to 44.9% in Malaysia. The mean dose of LAI antipsychotics, as mg/day approximately equivalent to orally administered chlorpromazine as a standard comparator (CPZ-eq) averaged 231 [CI: 184-278] mg/day. However, the total daily exposure to all antipsychotic drugs averaged 451 [395-507] CPZ-eq mg/day, or nearly twice-more than the dose of LAI agents only, owing to the use of more than one type of drug in many subjects (Table 2).

Subjects receiving any LAI (with or without oral supplements) vs only orally administered antipsychotics were compared (Table 2). Use of LAI agents differed from oral treatment only in several ways: (a) *demographic factors* (older age, and a tendency toward more men than women), (b) *illness features* (multiple hospitalizations, disorganized and negative symptoms, verbal and physical aggression, but not in the presence of hallucinations or delusions), (c) psychosocial *functional status* (superior functioning), (d) *treatment* characteristics (use of more than one antipsychotic, higher antipsychotic doses), and (e) risks of *adverse effects* (higher BMI, more tremor and rigidity).

Multivariable logistic regression modeling identified several factors that were significantly and independently associated with the use of LAI antipsychotics. These included longer duration of illness, disorganized behavior, lack of negative symptoms, and better social-occupational functioning (Table 3).

We also compared characteristics of subjects who received FGAs or SGAs in LAI formulations (Table 4). Those treated with FGA-LAI agents were significantly more likely to be male, currently hospitalized, and to show more disorganized speech and behavior, with more verbal or physical aggression. They were also more likely to be given more than one antipsychotic drug and at higher average total daily CPZ-eq doses.

Based again on multivariable logistic regression modeling, use of FGA-LAIs vs SGA-LAIs were independently and significantly associated with: male sex, verbal aggression, disorganized speech, and current psychiatric hospitalization (Table 5).

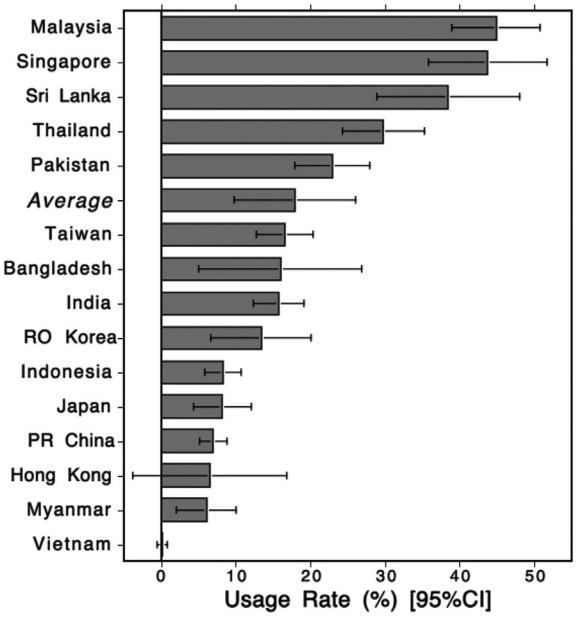

FIGURE 1 Rates of usage of long-acting injected antipsychotic drugs as percentage of treated schizophrenia patients in 15 Asian countries, with 95% confidence intervals, ranked in descending order

4 | DISCUSSION

Several findings from this large multicenter study of the use of LAI antipsychotic drugs to treat schizophrenia patients in 15 countries and region in Asia are noteworthy. Rates of use of such agents averaged 17.9%, but varied by more than 40-fold among different countries, and were greatest in Malaysia and Singapore, and lowest in Vietnam and China (Table 1). Subjects given LAI antipsychotics were older, males, had more years of illness with multiple hospitalizations, had more disorganized behavior, showed more verbal and physical aggression, and had better psychosocial functioning. They were also more likely to receive more than one antipsychotic drug (usually supplemented with oral medication), and higher total daily CPZ-eq doses, and are more likely to experience more adverse neurological effects, including more tremor and muscular rigidity (Tables 2 and 3). We also identified significant differences between subjects treated with older (FGA) vs newer (SGA) antipsychotic agents in LAI preparations, including more men, disorganized speech, verbal aggression, and current hospitalization among those given FGA-LAIs(Tables 4 and 5).

The present findings can be compared to a similar, decade earlier study in six Asian countries (Sim et al., 2004). Overall, the current findings indicate a modest increase in use of LAI agents, from 15.3% to 17.9%, and from 15.3% (368 out of 2399 subjects) to 16.0% (171 out of 1066 subjects) among the same six countries sampled at both times. Our observed average prevalence of use of depot antipsychotics in Asia is consistent with recent rates averaging 19.9% in several Western countries: USA (8%), Denmark (16.7%), UK (35%) (Barnes et al., 2009; Potkin et al., 2013; Sneider et al., 2015). As in the present findings (Table 1), marked differences between countries and regions also have been noted in other parts of the world (Hálfdánarson et al., 2017; Oteri et al., 2016). Reasons for both the generally limited acceptance of LAI antipsychotics and the high regional differences in their use are not entirely clear. Patient factors including age, sex, and clinical characteristics may contribute. For example, patients who are unreliably adherent to prescribed oral treatments and present disruptive or threatening behavior are more likely to receive injectable drugs (Arango, Bombín, & González-

TABLE 2 Comparison of patients treated with LAI versus oral antipsychotics

Factor	LAI	Oral	Statistic (*t*, *U* or χ^2) or OR	*P*-value
Subjects (n)	638	2919	-	-
Male sex (%)	62.2 [58.3-66.0]	58.2 [56.4-60.0]	1.18	.06
Current age (years)	41.1 ± 11.8	39.6 ± 13.0	2.85	.004
CPZ-eq dose (mg/day)	535 ± 372	404 ± 351	8.14	<.001
Given ≥2 antipsychotics (%)	77.4 [74.0-80.6]	32.0 [30.3-33.7]	7.29 [5.96-8.92]	<.001
Body-Mass Index (kg/m^2)	24.5 ± 4.99	23.9 ± 4.62	3.01	.003
Hospitalized (%)	49.8 [45.9-53.8]	52.3 [50.5-54.2]	0.91	.25
First admission (%)	21.0 [16.7-25.9]	31.6 [29.3-34.0]	0.58	<.001
In remission (%)	51.3 [47.3-55.2]	48.5 [46.6-50.3]	1.12 [0.94-1.33]	.20
Delusional (%)	45.5 [41.5-49.4]	41.7 [39.9-43.5]	1.17 [0.98-1.39]	.08
Hallucinating (%)	47.6 [43.7-51.6]	45.9 [4.1-47.84]	1.07 [0.90-1.27]	.43
Disorganized speech (%)	30.3 [26.7-34.0]	28.9 [27.3-30.6]	1.07 [0.88-1.28]	.51
Disorganized behavior (%)	21.9 [18.8-25.4]	16.5 [15.2-17.9]	1.42 [1.15-1.75]	.001
Negative symptoms (%)	27.4 [24.0-31.1]	37.5 [35.839.3]	0.63 [0.52-0.76]	<.001
Dysfunctional (%)	38.6 [34.8-42.5]	46.7 [44.9-48.6]	0.72 [0.60-0.85]	<.001
Verbal aggression (%)	29.6 [26.1-33.3]	23.9 [22.4-25.5]	1.34 [1.11-1.62]	.003
Physical aggression (%)	25.2 [21.9-28.8]	19.5 [18.1-21.0]	1.39 [1.14-1.70]	.001
Affective symptoms (%)	11.8 [9.36-14.5]	11.0 [9.92-12.2]	1.07 [0.82-1.40]	.60
Extrapyramidal syndromes (%)				
Any	35.3 [31.6-39.2]	28.3 [26.7-30.0]	1.38 [1.15-1.66]	.001
Tremor	25.6 [22.2-29.2]	17.1 [15.7-18.5]	1.67 [1.36-2.04]	<.001
Rigidity	14.3 [11.7-17.3]	10.5 [9.43-11.7]	1.42 [1.10-1.83]	.007
Akathisia	5.81 [4.10-7.95]	6.95 [6.03-7.95]	0.83 [0.57-1.19]	.30
Dystonias	1.61 [0.78-2.95]	2.28 [1.76-2.90]	0.70 [0.36-1.38]	.30
Tardive dyskinesia	1.94 [1.00-3.36]	1.70 [1.26-2.25]	1.14 [0.60-2.16]	.69
Akinesia	6.14 [4.38-8.33]	6.20 [5.34-7.17]	0.99 [0.69-1.42]	.95

Note: Data are means ± SD, or % [with 95%CI], comparing schizophrenia patients treated with long-acting injected (LAI), alone or with orally administered supplements vs oral antipsychotic drugs only. CPZ-eq = approximate mg/day equivalent of orally administered chlorpromazine. Dysfunction is for social or occupational functions.

TABLE 3 Factors associated with treatment with LAI vs oral antipsychotics

Factor	OR [95%CI]	Wald test score	*P*-value
Duration of illness			
(vs >20 years)	-	28.5	<.001
<3 months	2.33 [0.62-8.74]	1.57	.22
3-6 months	1.36 [0.35-5.35]	0.20	.66
0.5-1.0 year	4.35 [1.50-12.7]	7.28	.007
1-5 years	5.38 [1.85-15.7]	9.53	.002
5-10 years	7.45 [2.56-21.7]	13.6	<.001
10-20 years	7.47 [2.48-22.5]	12.8	<.001
Disorganized behavior	1.87 [1.41-2.49]	18.6	<.001
Negative symptoms	0.488 [0.365-0.653]	23.3	<.001
Dysfunction	0.554 [0.424-0.723]	18.9	<.001

Note: OR = Odds Ratio [with 95% CI] for treatment with LAI vs oral antipsychotics. Other factors not significantly associated with antipsychotic treatment type include: male sex, being in a first lifetime hospitalization, current age, currently in clinical remission, presence of delusions, hallucinations, disorganized speech, verbal aggression, physical aggression, affective symptoms, or other symptoms. Disorganized behavior includes catatonic features.

TABLE 4 Characteristics of schizophrenia patients given first- or second-generationlong-acting injected (LAI) antipsychotic drugs

Factors	First-generation(FGA-LAI)	Second generation (SGA-LAI)	Statistics (*t*, *U* or χ^2) or OR	*P*-value
Subjects (n; % of LAIs)	543 (85.0)	95 (14.9)	-	-
Usage rate (% of all cases)	15.3 [14.1-16.5]	2.67 [2.17-3.26]		
Age (years)	41.2 ± 11.7	41.0 ± 12.9	0.143	.89
Male sex (%)	64.5 [60.2-68.5]	49.5 [39.1-59.9]	1.85 [1.19-2.87]	.005
Given ≥2 antipsychotics	82.9 [79.6-86.1]	46.3 [36.0-56.8]	5.61 [3.54-8.89]	<.001
Total CPZ-eq dose (mg/day)	551 ± 380	446 ± 302	2.99	.003
Illness duration (years)	5.49 ± 1.25	5.53 ± 1.37	1.23 [1.18-1.28]	.77
Body-Mass Index (kg/m^2)	24.4 ± 4.97	25.2 ± 5.05	1.55	.12
Hospitalized (%)	52.1 [47.8-56.4]	36.8 [27.2-47.4]	1.87 [1.19-2.83]	.006
In first hospitalization (%)	20.4 [17.1-24.1]	25.7 [16.9-35.2]	0.74 [0.33-1.69]	.47
Currently in remission (%)	50.3 [46.0-54.6]	56.8 [46.3-67.0]	0.77 [0.50-1.19]	.24
Delusional (%)	44.8 [40.5-49.0]	49.5 [39.1-59.9]	0.83 [0.54-1.28]	.39
Hallucinating (%)	47.7 [43.4-52.0]	47.4 [37.0-57.4]	1.01 [0.66-1.57]	.95
Disorganized speech (%)	33.0 [29.0-37.1]	14.7 [8.30-23.5]	2.85 [1.57-5.16]	<.001
Disorganized behavior (%)	23.4 [19.9-27.2]	13.7 [7.49-22.3]	1.93 [1.04-3.57)	.04
Negative symptoms (%)	26.3 [22.7-30.3]	33.7 [24.3-44.1]	0.70 [0.44-1.12]	.14
Dysfunctional (%)	38.3 [34.2-42.5]	40.0 [30.1-50.6]	0.93 [0.60-1.45]	.75
Verbal aggression (%)	33.0 [29.0-37.1]	10.5 [5.16-18.5]	4.18 [2.12-8.24]	<.001
Physical aggression (%)	27.6 [23.9-37.1]	11.6 [5.92-19.8]	2.92 [1.51-5.62]	.001
Affective symptoms (%)	11.0 [8.54-14.0]	15.8 [9.12-24.7]	0.66 [0.36-1.22]	.19
Extrapyramidal syndromes (%)				
Any	36.3 [32.2-40.6]	29.3 [20.3-39.8]	1.37 [0.85-2.23]	.20
Rigidity	15.1 [12.2-18.4]	9.89 [4.62-17.9]	1.62 [0.78-3.36]	.19
Akinesia	6.63 [4.66-9.10]	3.30 [0.69-9.33]	2.08 [0.63-6.92]	.22
Tremor	26.2 [22.5-30.1]	22.0 [14.0-31.9]	1.26 [0.74-2.14]	.40
Akathisia	5.28 [3.54-7.55]	8.89 [3.92-16.7]	0.57 [0.25-1.30]	.18
Dystonia	1.89 [0.91-3.44]	0.00 [0.00-4.02]	-	-
Tardive dyskinesia	1.89 [0.91-3.44]	2.22 [0.27-7.80]	-	-
Systemic adverse effects (%)				
Excess sedation	12.0 [9.35-15.1]	5.56 [1.83-12.5]	2.32 [0.91-5.93]	.07
Weight-gain	12.7 [9.80-16.1]	12.5 [641-21.3.]	1.02 [0.51-2.03]	.96
Constipation	23.1 [19.6-27.0]	17.6 [10.4-27.0]	1.41 [0.79-2.51]	.24
Sialorrhea	14.3 [11.4-17.6]	7.69 [3.15-15.2]	2.00 [0.89-4.49]	.09
Dry mouth	16.9 [13.8-20.4]	11.0 [5.40-19.3]	1.65 [0.82-3.31]	.16
Urinary hesitancy	0.77 [0.21-1.97]	3.26 [0.68-9.23]	-	-
Blurred vision	5.58 [3.77-7.91]	1.10 [0.03-5.97]	-	-
Postural hypotension	5.35 [3.59-7.64]	0.00 [0.00-0.00]	-	-
Impaired glucose tolerance	9.00 [6.45-12.2]	3.53 [0.73-9.97]	2.71 [0.82-8.98]	.09
Hypercholesterolemia	12.8 [9.74-16.5]	5.95 [1.96-13.3]	2.33 [0.90-6.02]	.07

Note: Data are means ± SD or % or OR [95%CI]. CPZ-eq = Approximate oral chlorpromazine-equivalent dose (mg/day).
Abbreviations: LAI, long-acting injected; OR, Odds ratio.

Salvador, 2006; Belli & Ural, 2012). In addition, it is likely that other factors including regional variances in healthcare systems such as availability of drugs, pharmaco-economics, and prescribing habits of psychiatrists may also play a role, including in Asian countries (Si et al., 2011).

In the present sample, there is only a 4% greater proportion of male patients given LAI antipsychotics (Table 2). In other studies, LAI treatment was considerably more likely to involve male patients (Decuypere, Sermon, & Geerts, 2017; Janzen, Bolton, Kuo, Leong, & Alessi-Severini, 2020; Ostuzzi et al., 2018). Of note, similar portions

TABLE 5 Factors associated with treatment with first- vs. second-generation. long-acting injected antipsychotic drugs

Factor	OR [95%CI]	Statistic	*P*-value
Male sex	2.22 [1.38-3.58]	10.85	.001
Verbal aggression	3.63 [1.60-8.24]	9.48	.002
Disorganized speech	2.21 [1.13-4.31]	5.38	.02
Hospitalized	1.73 [1.03-2.92]	4.26	.03

of patients given LAI (49.8%) and oral antipsychotics (52.3%) were currently hospitalized (Table 2), if a major reason to employ LAI treatments is to limit treatment nonadherence among ambulatory patients (Panish, Karve, Candrilli, & Dirani, 2013; Verdoux et al., 2000; West et al., 2008). Presumably, however, many patients required hospitalization due to morbidity arising from treatment nonadherence, and may have been started on a LAI regimen in anticipation of aftercare. More broadly, important questions remain about the relative clinical value of relying on LAI antipsychotic treatment compared to oral medication, perhaps supplemented with closer clinical support and supervision, such as with assertive community treatment (ACT) programs (Barnes et al., 2009; Jaeger & Rossler, 2010).

Particularly intriguing findings are that participants treated with modern SGAs in LAI formulations were 1.79-times*less* likely to receive multiple antipsychotic drugs, and were exposed to 1.24-fold lower total daily CPZ-eq doses than those given older FGAs (Table 4). That is, the overall greater use of multiple antipsychotics and higher total daily dose-exposure with LAI agents in general (Table 2) may be limited by use of SGA-LAIs. Similar findings have been reported previously (Ostuzzi et al., 2018). These differences may suggest hoped-for clinical superiority of SGAs over FGAs, which has been difficult to prove (Baldessarini, 2013). Despite the lower average dosing with SGA-LAIs vs FGA-LAIs, risks of neurological and systemic adverse effects were generally quite similar (Table 4). Lack of longitudinal data preclude assessment of potentially important differential effects of LAI vs oral, and of SGA-LAI vs FGA-LAI treatments on morbidity and other critical aspects of clinical outcome. In addition, it is likely that socioeconomic factors may have a major impact on rates of utilization of older vs newer, more expensive pharmacotherapy which can also impact clinical outcome (Nielsen, Jensen, Friis, Valentin, & Correll, 2015; Si et al., 2011).

4.1 | Limitations

There were several strengths and limitations to this study. It involved a large and broadly representative sampling from 15 Asian countries and region, with standardized methods of clinical assessment and data-management. Major limitations include lack of extensive sampling from well-characterized locations within individual countries to address the effects of such factors as rural vs urban settings, academic vs clinical healthcare programs, and the number of subjects treated with LAI agents is small for some countries. Moreover, the study was cross sectional in nature and future efforts would want to consider following up the subjects over their illness course and treatment prospectively. Also, we did not capture details of healthcare financing across countries which can be further examined in the context of intercountry variations in psychotropic prescription patterns including depot antipsychotics.

4.2 | Conclusion

In conclusion, we found that the rate of use of LAI antipsychotic preparations had increased modestly (1.17-fold), from 15.3% to 17.9% of treated schizophrenia patients over the last 12 years in Asia, with very wide regional variations as have been reported in other world regions. The use of LAI treatment was associated with more polytherapy and higher average total daily antipsychotic drug doses, although less with SGA-LAIs than with FGA-LAIs. These findings behoove clinicians to be mindful when considering management options including LAI antipsychotic preparations in terms of balancing clinical benefits vs risks over the treatment course of a potentially crippling illness.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Chao T. Tang, Ee C. Chua, Qian H. Chew, and Kang Sim have made substantial contributions to conception and design of this project theme, acquisition of data, analysis and interpretation of the data, drafting of the manuscript, revision of the paper for important intellectual content, given final approval of the version to be published and agreed to be accountable for all aspects of the work; all other co-authors have made substantial contributions to acquisition of data or analysis and interpretation of the data, revision of the paper for important intellectual content, given final approval of the version to be published and agreed to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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