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Prescription Patterns for Bipolar Disorder in Asian Countries: Findings from Research on Asian Prescription Pattern-Bipolar Disorder

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Objective: Pharmacotherapy including mood stabilizers and antipsychotics are frequently used in bipolar disorder (BD); however, the lack of consensus regarding the definition of polypharmacy hinders conducting comparative studies across different settings and countries. Research on Asian Prescription Pattern (REAP) is the largest and the longest lasting international collaborative research in psychiatry in Asia. The objective of REAP BD was to investigate the prescription patterns of psychotropic medications across Asian countries. The rates of polypharmacy and psychotropic drug load were also analyzed.

Methods: The data collection was web-based. Prescription patterns were categorized as (1) mood stabilizer monotherapy: one mood stabilizer; (2) antipsychotic monotherapy: one antipsychotic; (3) simple polypharmacy: one mood stabilizer and one antipsychotic; and (4) complex polypharmacy: ≥ 2 mood stabilizers or/and antipsychotics. The psychotropic drug load in each patient was calculated using the defined daily dose method.

Results: Among 2003 patients with BD (52.1% female, 42.4 years) from 12 countries, 1,619 (80.8%) patients received mood stabilizers, 1,644 (82.14%) received antipsychotics, and 424 (21.2%) received antidepressants, with 14.7% mood stabilizer monotherapy, 13.4% antipsychotic monotherapy, 48.9% simple polypharmacy, 20.3% complex polypharmacy, and 2.6% other therapy. The average psychotropic drug load was 2.05 ± 1.40. Results varied widely between countries.

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Conclusion: Over 70% of psychotropic regimens involved polypharmacy, which accords with the high prevalence of polypharmacy in BD under a permissive criterion (2 or more core psychotropic drugs) worldwide. Notably, ≥ 80% of our sample received antipsychotics, which may indicate an increasing trend in antipsychotic use for BD treatment.

KEY WORDS: Bipolar disorder; Polypharmacy; Psychotropic drug load; Antipsychotics; Mood stabilizers.

INTRODUCTION

Bipolar disorder (BD) is a severe, recurring mental illness. Pharmacotherapy is crucial in the treatment of BD, supplemented by social and psychological interventions. Pharmaceutical treatments for BD are mood stabilizers and antipsychotics, which are sometimes combined with anxiolytics and hypnotics. In certain situations, patients are prescribed antidepressants. The movement side effects of second-generation antipsychotics (SGAs) are relatively minor; thus, they have even become the principal therapeutic agents employed to replace mood stabilizers [1,2]. Long-acting injection antipsychotics also have become more common [3]. The symptoms or signs and the course of BD are complicated, dynamic, and changeable regarding the illness course and phase. Furthermore, medication use differs in each phase. Despite the availability of numerous pharmacological textbooks and treatment guidelines for a specific disorder [4,5], wide variations exist in selecting drugs and dosages between different physicians and also different countries [6,7].

Polypharmacy-related studies are much less popular for BD than for schizophrenia [8,9]; especially the definitions of polypharmacy in BD are vague and inconsistent. In a review, Fornaro *et al.* [10] discussed the definition of polypharmacy in BD; most definitions of polypharmacy centered on the use of 2 or more psychotropic drugs at once, and complex polypharmacy centered on the use of ≥ 4 psychotropic and non-psychotropic drugs at once. This type of classification is easily applicable in clinical practice but not feasible for scientific research because only mood stabilizers and antipsychotics are currently indicated for BD. Patients receiving antidepressants, anxiolytics, or antihypertensives should not be included in polypharmacy.

Research on Asian Prescription Patterns (REAP) is an international collaborative consortium for studying the prescription patterns of psychotropic drugs across countries (http://reap.asia/index.html). The aim of this study (REAP-BD) was to survey prescription patterns for BD in Asian countries. Prescriptions for mood stabilizers, antipsychotics, and other psychotropic drugs were included in the investigation of prescription patterns to reveal the rate of polypharmacy, the dosage of each class of drug, the different proportions of mood stabilizers, the rate of first-generation antipsychotics (FGAs) and SGAs, and other combined medications.

METHODS

Design and Participants

A convenience sampling method was used to enroll study patients. Patients with BD who were undergoing pharmacotherapy could be included in the survey. Participating psychiatrists assessed patients according to their clinical features and assigned them a status based on ICD-10-CM codes F31.0 to F31.9. An online website-based data key-in system was used for data collection. The research protocol can be accessed at http://www.reap.asia/pdf/reap_bd_protocol.pdf. In brief, data regarding daily medications prescribed for treating inpatients or outpatients with BD, including mood stabilizers, antipsychotics, antidepressants, anxiolytics, hypnotics, and other concomitant medications, as well as demographics and laboratory tests, were collected.

Classification of Polypharmacy in BD

Because mood stabilizers and some antipsychotics are indicated for treating BD, defining polypharmacy is complex. In the present study, core medications for BD were defined as mood stabilizers and antipsychotics, and other psychotropic drugs, such as antidepressants, hypnotics, and anxiolytics, were categorized as peripheral medications. The most commonly accepted definition of polypharmacy in schizophrenia is the simultaneous use of 2 or more antipsychotics [9]; thus, we proposed polypharmacy in BD as the simultaneous use of 2 or more core medications. To simplify operational criteria, prescription patterns for BD monotherapy and polypharmacy were categorized as follows: (1) mood stabilizer monotherapy:

only one mood stabilizer used; (2) antipsychotic monotherapy: only one antipsychotic used; (3) simple polypharmacy: one mood stabilizer and one antipsychotic used; and (4) complex polypharmacy: ≥ 2 mood stabilizers or/and antipsychotics used. The use of long-acting injectable antipsychotics will be categorized as a type of antipsychotic. The use of antidepressants, anxiolytics and hypnotics was also recorded, and was classified as combined medications.

Psychotropic Drug Load to Indicate the Dosage Used

Conventionally, a chlorpromazine equivalent is used to compare the therapeutic dose of an antipsychotic [11,12]. Since the core medications for BD including antipsychotic and mood stabilizers, the Anatomical Therapeutic Chemical (ATC) Classification System (i.e., the ATC/DDD [defined daily dose] Index 2016 [accessed May 1, 2019]) [13], was employed to calculate the drug load to compare the dosage used across the different categories of psychotropic drugs. For instance, the mood stabilizer load was calculated using the sum of the prescribed daily dose of each mood stabilizer divided by its DDD. The value obtained reflected the quantity of mood stabilizer received by a patient, and the psychotropic drug load (PDL) was used to represent the psychotropic medication (antipsychotics, mood stabilizers, antidepressants, anxiolytics and hypnotics) quantity prescribed to treat a mental disorder. For lithium, the suggested DDD was 24 mmol, where lithium carbonate (Li_2CO_3) weight is 73.891 g/mol. As 73.891 g/mol × 24 mmol / 2 = 886.692 mg, in the present study, 900 mg was used as the DDD for convenient calculation.

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RESULTS

In total, 2003 patients with BD (70.3% outpatients; 52.1% female) were enrolled from 13 countries or regions. The numbers and demographics of each country are presented in Table 1, listed in the order of the number of patients enrolled. The mean age was 42.4 ± 15.2 years, with the oldest patients in Singapore (56.2 ± 15.5) and the youngest in Myanmar (30.8 ± 9.0). The mean body weight was 67.1 ± 14.0 kg, with the highest patient weights in

Table 1. Patient numbers and demographics for each country

Variable	South Korea (n = 408)	China (n = 321)	Taiwan (n = 246)	Pakistan (n = 214)	India (n = 202)	Malaysia (n = 182)	Japan (n = 122)	Thailand (n = 91)	Indonesia (n = 81)	Sri Lanka (n = 40)	Singapore (n = 36)	Hong Kong (n = 30)	Myanmar (n = 30)	Total (n = 2,003)
Sex														
Male	157	151	123	132	119	94	59	30	33	14	18	12	16	958
Female	251	170	123	82	83	88	62	61	48	26	18	18	14	1,044
Age (yr)	42.7 ± 15.3	39.7 ± 14.5	46.4 ± 14.1	33.6 ± 11.4	46.3 ± 14.7	42.2 ± 12.5	56.2 ± 15.6	39.6 ± 17.9	35.0 ± 12.6	45.1 ± 14.6	45.7 ± 12.1	48.6 ± 16.0	30.8 ± 9.0	42.4 ± 15.2
Weight (kg)	64.9 ± 12.3	67.9 ± 12.4	68.5 ± 16.4	65.2 ± 13.3	70.0 ± 12.8	75.0 ± 15.9	61.0 ± 13.3	64.6 ± 13.7	69.1 ± 14.5	58.6 ± 13.2	71.2 ± 14.5	NA	59.3 ± 9.2	67.1 ± 14.0
BMI (kg/m^2)	24.1 ± 4.1	24.3 ± 3.9	25.6 ± 5.3	23.9 ± 4.9	25.8 ± 4.3	27.7 ± 5.3	23.2 ± 3.9	24.6 ± 4.7	26.8 ± 5.2	24.5 ± 4.8	26.4 ± 5.1	NA	22.3 ± 2.9	24.9 ± 4.7

Values are presented as number only or mean ± standard deviation.
NA, not available; BMI, body mass index.

Table 2. Present states of illness for each country

Variable	South Korea (n = 408)	China (n = 321)	Taiwan (n = 246)	Pakistan (n = 214)	India (n = 202)	Malaysia (n = 182)	Japan (n = 122)	Thailand (n = 91)	Indonesia (n = 81)	Sri Lanka (n = 40)	Singapore (n = 36)	Hong Kong (n = 30)	Myanmar (n = 30)	Total (n = 2,003)
Remission (F31.7)	154 (37.7)	65 (20.2)	75 (30.5)	39 (18.2)	177 (87.6)	111 (61.0)	21 (17.2)	28 (30.8)	22 (27.2)	12 (30.0)	22 (61.1)	12 (40.0)	6 (20.0)	744 (37.1 ± 21.0)
Manic (F31.0, F31.1, & 31.2)	102 (25.0)	151 (47.0)	85 (34.6)	126 (58.9)	14 (6.9)	16 (8.8)	64 (52.5)	12 (13.2)	31 (38.3)	6 (15.0)	11 (30.6)	7 (23.3)	23 (76.7)	648 (32.4 ± 21.1)
Depressive (F31.3, F31.4, & F31.5)	55 (13.5)	68 (21.2)	39 (15.9)	31 (14.5)	10 (5.0)	12 (6.6)	20 (16.4)	15 (16.5)	15 (18.5)	18 (45.0)	2 (5.6)	2 (6.7)	1 (3.3)	288 (14.4 ± 10.9)
Mixed (F31.6)	21 (5.1)	16 (5.0)	18 (7.3)	18 (8.4)	1 (0.5)	6 (3.3)	5 (4.1)	2 (2.2)	8 (9.9)	4 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	99 (4.9 ± 3.2)
Other	76 (18.6)	21 (6.5)	29 (11.8)	0 (0.0)	0 (0.0)	37 (20.3)	12 (9.8)	34 (37.4)	5 (6.2)	0 (0.0)	1 (2.8)	9 (30.0)	0 (0.0)	224 (11.2 ± 11.7)

Values are presented as number (%) or number (mean ± standard deviation%).

Table 3. Numbers and rates of psychotropic drug use for each country

Variable	South Korea (n = 408)	China (n = 321)	Taiwan (n = 246)	Pakistan (n = 214)	India (n = 202)	Malaysia (n = 182)	Japan (n = 122)	Thailand (n = 91)	Indonesia (n = 81)	Sri Lanka (n = 40)	Singapore (n = 36)	Hong Kong (n = 30)	Myanmar (n = 30)	Total (n = 2,003)
Mood stabilizers used	365 (89.5)	265 (82.6)	177 (72.0)	172 (80.4)	186 (92.1)	155 (85.2)	90 (73.8)	54 (59.3)[b]	60 (74.1)	16 (40.0)[b]	27 (75.0)	24 (80.0)	28 (93.3)	1,619 (80.8 ± 14.4)
Antipsychotics used	372 (91.2)	293 (91.3)	196 (79.7)	158 (73.8)	148 (73.3)	160 (87.9)	92 (75.4)	53 (58.2)[b]	67 (82.7)	31 (77.5)	30 (83.3)	16 (53.3)[b]	28 (93.3)	1,644 (82.1 ± 12.2)
Antidepressants used	79 (19.4)	64 (19.9)	65 (26.4)	23 (10.7)	38 (18.8)	23 (12.6)	33 (27.0)	33 (36.3)[a]	33 (40.7)[a]	17 (42.5)[a]	6 (16.7)	9 (30.0)	1 (3.3)	424 (21.2 ± 11.8)
Anxiolytics used	195 (47.8)	68 (21.2)[b]	120 (48.8)	162 (75.7)	15 (7.4)[b]	25 (13.7)[b]	33 (27.0)[b]	51 (56.0)	31 (38.3)	15 (37.5)	11 (30.6)	7 (23.3)	13 (43.3)	746 (37.2 ± 18.6)
Hypnotics used	35 (8.6)	24 (7.5)	112 (45.5)[a]	0 (0.0)	2 (1.0)	10 (5.5)	74 (60.7)[a]	0 (0.0)	3 (3.7)	2 (5.0)	6 (16.7)	4 (13.3)	0 (0.0)	272 (13.6 ± 20.0)
Psychotropic drug load	2.28 ± 1.34	2.35 ± 1.35	2.41 ± 1.77	1.90 ± 1.37	1.49 ± 0.88	1.94 ± 1.25	2.38 ± 1.86	1.31 ± 0.91	1.49 ± 0.91	1.87 ± 1.30	2.00 ± 1.43	1.47 ± 1.30	1.85 ± 0.95	2.05 ± 1.40

Values are presented as number (%), number (mean ± standard deviation%), or mean ± standard deviation.
[a,b]Contain more than and less than 1 standard deviation, respectively.

Table 4. Comparison of prescription patterns between countries

Variable	South Korea (n = 408)	China (n = 321)	Taiwan (n = 246)	Pakistan (n = 214)	India (n = 202)	Malaysia (n = 182)	Japan (n = 122)	Thailand (n = 91)	Indonesia (n = 81)	Sri Lanka (n = 40)	Singapore (n = 36)	Hong Kong (n = 30)	Myanmar (n = 30)	Total (n = 2,003)
Simple polypharmacy	193 (47.3)	211 (65.7)[a]	108 (43.9)	90 (42.1)	107 (53.0)	111 (61.0)	36 (29.5)[b]	30 (33.0)[b]	40 (49.4)	6 (15.0)[b]	16 (44.4)	10 (33.3)	22 (73.3)[a]	980 (48.9 ± 15.8)
Complex polypharmacy	154 (37.7)[a]	41 (12.8)	34 (13.8)	48 (22.4)	28 (13.9)	28 (15.4)	40 (32.8)[a]	3 (3.3)[b]	7 (8.6)[b]	9 (22.5)	9 (25.0)	2 (6.7)[b]	4 (13.3)	407 (20.3 ± 10.1)
Mood stabilizer monotherapy	31 (7.6)	22 (6.9)	41 (16.7)	49 (22.9)	53 (26.2)[a]	20 (11.0)	20 (16.4)	22 (24.2)	13 (16.0)	4 (10.0)	5 (13.9)	13 (43.3)[a]	2 (6.7)	295 (14.7 ± 10.2)
Antipsychotic monotherapy	28 (6.9)	42 (13.1)	55 (22.4)	21 (9.8)	13 (6.4)	21 (11.5)	20 (16.4)	20 (22.0)	20 (24.7)[a]	17 (42.5)[a]	5 (13.9)	4 (13.3)	2 (6.7)	268 (13.4 ± 10.0)
Antidepressant monotherapy	2 (0.5)	5 (1.6)	5 (2.0)	5 (2.3)	1 (0.5)	1 (0.5)	4 (3.3)	12 (13.2)[a]	1 (1.2)	4 (10.0)	1 (2.8)	1 (3.3)	0 (0.0)	42 (2.1 ± 4.0)
Neither	0 (0.0)	0 (0.0)	3 (1.2)	1 (0.5)	0 (0.0)	1 (0.5)	2 (1.6)	4 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.5 ± 1.6)

Values are presented as number (%) or number (mean ± standard deviation%).
[a,b]Contain more than and less than 1 standard deviation, respectively.

Malaysia (75.0 ± 15.9) and the lowest in Sri Lanka (58.6 ± 13.2). The mean body mass index was 24.9 ± 4.7. Table 2 summarizes the stages of illness at enrollment. The largest proportion of patients were in the remission phase (37.1%), followed by manic (32.4%), depressed (14.4%), others (11.2%), and mixed (4.9%). Regarding the illness course pattern, 43% of patients presented with mania or hypomania, followed by depression and a euthymic interval (MDI), and 30% of patients presented with depression, followed by mania or hypomania (DMI). The remaining participants exhibited unknown patterns. Table 3 illustrates the numbers and rates of psychotropic drugs used. Over 80% of patients were prescribed mood stabilizers or antipsychotics, 21.2% antidepressants, 37.2% anxiolytics, and 13.6% hypnotics. Valproic acid (47.2%) was the most prescribed mood stabilizer, followed by lithium (28.5%), carbamazepine (6.7%), and lamotrigine (1.1%), and most prescribed antipsychotics were quetiapine (33.1%), olanzapine (19.6%), risperidone (14.4%), and aripiprazole (11.3%). The total PDL was 2.05 ± 1.40, with a median drug load of 0.67 for mood stabilizers, 0.8 for SGAs, 0.50 for FGAs, 0.40 for anxiolytics, and 1.00 for hypnotics.

Table 4 presents the prescription pattern across countries. The most common prescription patterns were simple polypharmacy (48.9% ± 15.8%), followed by complex polypharmacy (20.3% ± 10.1%), mood stabilizer monotherapy (14.7% ± 10.2%), antipsychotic monotherapy (13.4% ± 10.0%), and antidepressant monotherapy (2.1% ± 4.0%). Only 11 patients received neither mood stabilizers nor antipsychotics. Table 5 compares the psychotropic drug use and prescription pattern between different BD phases (diagnoses F31.8 and F31.9 excluded, n = 1,779).

DISCUSSION

This is the first comparative study of prescription patterns in patients with BD across Asian countries. The number of participants and course phases differed considerably between countries; thus, the entire group was first analyzed and results were then compared between countries.

Notably, approximately 82.1% of patients were receiving antipsychotics as the first choice of medications (67.6% of SGA, 6.9% of FGA, and 7.6% of both). No differences were noted in the use of antipsychotics between different illness phases, except slightly less in depressive

Table 5. Comparison of psychotropic drug use and prescription patterns between different bipolar disorder phases

Variable	Remission (n = 744)	Manic (n = 648)	Depressive (n = 288)	Mixed (n = 99)	Total (n = 1,779)
Mood stabilizers	628 (84.4)	553 (85.3)	189 (65.6)	75 (75.8)	1,445 (81.2)
Antipsychotics	598 (80.4)	557 (86.0)	222 (77.1)	90 (90.9)	1,467 (82.5)
Antidepressants	136 (18.3)	53 (8.2)	142 (49.3)	30 (30.3)	361 (20.3)
Anxiolytics	175 (23.5)	272 (42.0)	144 (50.0)	54 (54.5)	645 (36.3)
Hypnotics	66 (8.9)	98 (15.1)	59 (20.5)	16 (16.2)	239 (13.4)
Simple polypharmacy	397 (53.4)	340 (52.5)	108 (37.5)	45 (45.5)	890 (50.0)
Complex polypharmacy	118 (15.9)	156 (24.1)	46 (16.0)	29 (29.3)	349 (19.6)
Mood stabilizer monotherapy	130 (17.5)	78 (12.0)	49 (17.0)	7 (7.1)	264 (14.8)
Antipsychotic monotherapy	86 (11.6)	64 (9.9)	72 (25.0)	17 (17.2)	239 (13.4)
Antidepressant monotherapy	12 (1.6)	5 (0.8)	11 (3.8)	1 (1.0)	29 (1.6)
Neither	1 (0.1)	5 (0.8)	2 (0.7)	0 (0.0)	8 (0.4)

Values are presented as number (%).

phase (Table 5). The high rate of use of antipsychotics in the treatment of BD is similar to rates reported in Western countries. Hayes *et al.* [14] reported an increased prescription rate of antipsychotics from 14.2% to 41.9% from 1995 to 2009 in a very large British BD database. During this period, the use of SGA increased dramatically from 0% to 35%. A 17-year observational study in the United States reported that the prescription rate of antipsychotic medications per 100 persons increased from 3.25 to 6.18 among outpatients with BD, with SGA medications comprising the majority [15]. A 25-year Finnish nationwide cohort study of 18,018 patients with BD reported that 81.1% of participants took antipsychotics during follow-up [16]. Antipsychotics have primarily been used in manic or depressive phases with psychotic features in the past; however, an increasing number of antipsychotics, especially SGAs, are indicated for BD. Treatment guidelines for BD have suggested antipsychotics as the first-line choice of medication [17-19]. Several possible reasons exist for the increasing trend of antipsychotic prescription for patients with BD. First, SGAs with a lower propensity for extrapyramidal symptoms and the same or higher efficacy than typical antipsychotics have been introduced [20,21]. Second, psychiatric medications have become more acceptable in public opinion over the last 2 decades; thus, patients with BD are increasingly willing to use medications for depression, panic attacks, or other psychiatric problems to improve their quality of life [22]. Third, the role of psychotherapy appears to have become less prominent based on the declining number of psychiatrists specializing in psychotherapy and the decreased number of patients receiving psychotherapy over the last 2 decades [22,23].

Mood stabilizers are the gold standard for BD, both in acute and maintenance therapy. Our results also indicated that over 85% of patients were prescribed mood stabilizers in remission and manic phases, and less in mixed (75.8%) and depressive (65.6%) phases. For antipsychotics, more mixed and manic phases (> 85%) were prescribed and less in remission and depressive phased (Table 5).

Because of vague and inconsistent definitions, comparing the rates of polypharmacy in BD between studies is difficult. A post hoc report based on the STEP-BD study (n = 4,035) revealed that 21% of patients used 1 core medication (monotherapy, lithium, anticonvulsants, antidepressants, and antipsychotics), 28% used 2 (simple polypharmacy), 22% used 3, and 18% used 4 (complex polypharmacy); 12% did not use any core medications [24]. A comparative effectiveness trial of 482 patients with BD indicated that 43% had received complex polypharmacy over the study (≥ 4 types of lithium, antipsychotics, antidepressants, anticonvulsants, or anxiolytics) [25]. The authors concluded that patients with BD receiving complex polypharmacy were less likely to adhere to therapy and were less likely to achieve remission. A survey conducted in Poland in 127 patients with BD showed that 78 (61%) patients were prescribed 2 medications, 27 (21.3%) were prescribed 3, and one was prescribed 4 (mood stabilizers or SGA), with the combination of mood stabilizers and SGA was most commonly used (n = 61, 48%) [26]. Here we suggest that using the classification system defined in

this study, namely only mood stabilizer and antipsychotic regarded as core medication for BD, would enable easier comparison of the polypharmacy rate in BD between different studies and different phases (Table 5). By this definition, our results revealed more than 50% of simple polypharmacy was prescribed in remission and manic phase; and complex polypharmacy most popular in mixed phase (29.3%), mood stabilizer monotherapy least in mixed phase. It is interesting to note that antipsychotic monotherapy was most popular in depressive phase, followed by mixed phase. What is the ideal proportion of prescription pattern needs further investigation.

The majorities of treatment guidelines do not recommend antidepressants in BD, even in the depressed phase, or specify that they should be used with caution [18,19,27]. Lyall *et al.* [28] examined the trends of psychotropic drug use in a cohort of 23,135 patients with BD between 2009 and 2016 in Scotland and determined that the most common form of treatment was antidepressant monotherapy (24.96%), followed by antipsychotic monotherapy (12.94%), with only 5.90% of treated patients receiving lithium monotherapy. The authors concluded that their findings represented a gap between treatment guidelines and clinical practice, which was a cause of concern. Haeberle *et al.* [29], investigated a cohort of inpatients with bipolar depression (n = 2,246; 1994–2009) and reported that 85% of all patients received more than one class of psychotropic drugs; 74% received antidepressants in combination therapy, 55% received antipsychotics, 48% received anticonvulsants, and 33% received lithium. The rate of antidepressant use in our sample was 21.2%, and approximately half of them (49.3%) were in a depressed phase (Table 5). The rate of antidepressant monotherapy was only 2.1% (Table 4). These figures are more compatible with most treatment guidelines. Our results revealed that more females (22.9%) than males (19.2%) were prescribed antidepressants, which is in accordance with the findings of a study conducted by Weinstock *et al.* [30] (27% vs. 11%).

Our findings revealed differences in psychotropic drug prescription preferences between countries (Table 3). For instance, fewer mood stabilizers were prescribed in Thailand and Sri Lanka (less than one standard deviation), and fewer antipsychotics were prescribed in Thailand and Hong Kong, whereas more antidepressants were prescribed in Thailand, Indonesia, and Sri Lanka (more than one standard deviation). Interestingly, more hypnotics were prescribed in Taiwan and Japan compared with other countries. This preference for hypnotic prescriptions is also reported in the survey of schizophrenia in these 2 countries [31]. Regarding prescription patterns (Table 4), China and Myanmar had more simple polypharmacy by one standard deviation, whereas Korea and Japan had more complex polypharmacy. India and Hong Kong had more mood stabilizer monotherapy, whereas Indonesia and Sri Lanka had more antipsychotic monotherapy. Although the rate is still low (13.2%), Thailand had the most antidepressant monotherapy. Regarding PDL, Korea, China, Taiwan, and Japan prescribed higher doses of psychotropics than did other countries. For individual psychotropics drugs, only the load of hypnotics reached 1.0, and all others were below the suggested daily dose. This might have been because approximately 70% of patients received either simple or complex polypharmacy. Most studies have investigated the types of psychotropic drugs used but did not compare the dosage. By the application of PDD/DDD, it would be easier to compare the dosage of each psychotropic drug, or PDL in total. Different prescription pattern and dosage between countries might be attributed to psychiatrists' different training backgrounds, the availability of medications, civil culture, and the health insurance system of each country. Therefore, this topic warrants further investigation.

Tondo *et al.* [32] studied the major course pattern in 1,130 patients with BD and determined that 56.8% of patients could be characterized for major course patterns as either MDI or DMI, with similar proportions for each type. In our study, 73% of patients were characterized, with 43% of MDI and 30% of DMI. Whether ethnic or geographic latitude differences exist regarding the major course patterns of BD requires further investigation.

There are some limitations to the present study. First, the convenient sampling method may have incurred selection bias; thus, caution should be exercised when generalizing these results. Second, the cross-sectional design of the study means that no long-term prescription trend could be explored. Third, the number of patients enrolled from each country varied, and samples were not demographically representative. Furthermore, the sample was ethnically diverse. Nevertheless, the present study revealed a high proportion of antipsychotic use and a high rate of polypharmacy among patients with BD in Asia. Further

data from different countries would be needed to explore prescription trends worldwide.

In conclusion this survey delineated the different prescription patterns of pharmacotherapy on BD in 14 Asian countries. We proposed a new definition of polypharmacy for bipolar disorder for easier comparison between different study sites and course phases. Our results of different prescription patterns in specific course phases may offer a reference for clinical practitioners.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Designed the study, analyzed and interpreted data: Shih-Ku Lin, Shu-Yu Yang, and Naotaka Shinfuku. Data acquisition: All listed authors. Supervision: Mian-Yoon Chong and Norman Sartorius. Draft writing: Shih-Ku Lin. All authors have read and approved the revised manuscript.

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