BRIEF REPORT
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Examining Patterns of Polypharmacy in Bipolar Disorder: Findings from the REAP-BD, Korea

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Based on Korean data from the Research on Asian Psychotropic Prescription Pattern for Bipolar Disorder, this study tried to present prescription patterns in biopolar disorder (BD) and its associated clinical features. Based on the information obtained from the study with structured questions, the tendency of prescription pattern was studied and analyzed. Polypharmacy was predominant, including simple polypharmacy in 51.1% and complex polypharmacy in 34.2% of patients. Subjects associated with simple or complex polypharmacy were significantly younger, had higher inpatient settings, a larger portion of onset with manic episode, a shorter duration of untreated illness, a shorter duration of current episode, were more overweight, used less antidepressants and used more anxiolytics. These findings can suggest higher polypharmacy rate in more severe BD and highlight the necessity of monitoring the weight of subjects with polypharmacy.

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Key Words Polypharmacy, Bipolar disorder, Inpatient, Antidepressant.

INTRODUCTION

Bipolar disorder (BD) is a serious recurrent disorder, presenting as fluctuating mood and energy levels. It is the sixth most common burdensome disorder in the world.[1] Symptom severity differs greatly between individuals in terms of the duration of current episodes, the number of episodes, functional recovery after remission and the pattern of polarity. All of which contribute to the level of burden.[2-4] The complexity of BD's manifestation often makes treatment multifaceted and challenging to clinicians and while numerous clinical guidelines have been developed for the treatment.[5-8] The application of these guidelines in real world practice is poor, with complications occurring from differences in clinician's preference. Moreover, a wide spectrum of pharmacological regimens in BD can be attributed to sociocultural factors, ethnicity and insurance status.[9,10]

Considering the increased prescription of multiple psychotropics in BD patients, bringing adverse side effects, poor drug compliance, and drug interactions,[11,12] thorough investigation on prescription patterns in BD is necessary. The Research on Asian Psychotropic Prescription Pattern for Bipolar Disorder (REAP-BD) study would be of benefit to this investigation, due to its large sample size and large number of participating

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countries. Therefore, in this study, Korean data from the REAP-BD study is assessed in order to delineate polypharmacy prescription for Koreans with BD and related clinical features.

METHODS

Sixteen Asian countries and regions, including Bangladesh, China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Myanmar, Pakistan, Philippines, Singapore, Sri Lanka, Taiwan, Thailand and Vietnam, participated in the REAP-BD study, recruiting participants from September to December 2018. Under the direction of Taipei City Hospital, Taipei, Taiwan (receipt number: TCHIRB-10605117-E), every participating center received approval from their own institutional review boards. In order to investigate real clinical practice, simple inclusion criteria of a diagnosis of BD (F31) with the tenth revision of the International Classification of Diseases (ICD-10)[13] was applied. To include various clinical settings, 4 university-affiliated general hospitals, 2 mental hospitals, and 1 veteran health service medical center participated, overall enrolling 350 subjects up to October 8. For this study is still ongoing, we are planned to report the Korean data retrieved from REAP study, whose target number of participants was sufficiently met, as a preliminary report. Demographic and clinical characteristics (employment status, clinical history related to duration of episode, untreated illness duration, rapid cycling, seasonality, psychotropic prescription patterns, and other variables) were investigated. Representative investigators had participated in conferences before the opening of the survey to ensure consistent data collection and evaluation. The data collection was directed by the head center, the Taipei City Psychiatric Center, Taipei, Taiwan. The research protocols and informed consent forms were approved by the institutional review boards of all survey centers under the direction of Taipei City Hospital, Taipei, Taiwan (receipt number: TCHIRB-10605117-E). For its coherent evaluation, clarified definition and classification were applied. Psychotropic prescribing patterns were grouped by the Anatomical and Therapeutic Chemical Classification index of the World Health Organization Collaborating Center for Drug Statistics Methodology (with modification of grouping lithium into mood stabilizer (MS) and clonazepam into anxiolytics).[14] The MS or antipsychotic (AP) monotherapy/polypharmacy group included the MS or AP monotherapy group, MS polypharmacy group (using two or MSs) and the AP polypharmacy group (using two or more APs). A simple polypharmacy group was defined as subjects using one MS and one AP. While the complex polypharmacy group included subjects with three or more of either the MSs or APs.[15] Body mass index (BMI) calculated as weight (kg) divided by height $(m)^2$, classified 4 weight groups; underweight (<18.50), normal weight (18.50−24.99), overweight (25.00−29.99), and obese (>30).[16] Subjects with a history of four or more episodes of BD within one year were classified as "history with rapid cycling."[17] Seasonality patterns are defined as the peaks for manic episodes in spring to summer, depressive episodes in early winter, and mixed episodes in early spring to summer.[18]

Excluding 2 subjects with incomplete information on prescription, 348 subjects were included in our statistical analyses. Clinical and demographic profiles are shown as categorical and continuous variables, respectively. The clinical characteristics were compared among BD patients with MS or AP monotherapy/polypharmacy, simple polypharmacy, and complex polypharmacy. χ^2 tests for discrete variables and analyses of covariances for continuous variables were applied for analyses. Categorical variables were presented with frequencies and proportions, whereas continuous variables were presented as mean±standard deviation. Statistical significance was set at $p<0.05$ (two-tailed). IBM SPSS 24 (IBM Co., Armonk, NY, USA) was used for statistical analyses.

RESULTS

Of all subjects, 51.1% (n=178) were prescribed with simple polypharmacy, followed by 34.2% (n=119) with complex polypharmacy and 14.7% (n=51) with MS or AP monotherapy/polypharmacy. The number of subjects with MS monotherapy (n=27, 7.7%), AP monotherapy (n=14, 4.0%), MS polypharmacy (n=3, 0.9%) and AP polypharmacy (n=7, 2.0%) was so small.

As described in Table 1, subjects with MS or AP monotherapy/polypharmacy were significantly older than those with simple or complex polypharmacy, and their frequency of visiting outpatient clinics was higher than that of subjects in the other two groups. A shorter duration of untreated illness (<6 months) was mostly high in the simple polypharmacy group, followed by the MS or AP monotherapy/polypharmacy and complex polypharmacy groups. The proportion of manic episodes followed by depressive episodes in the long-term course was the highest in the complex polypharmacy group and smallest in the MS or AP monotherapy/polypharmacy group. The complex polypharmacy group showed shorter duration of current episode with great portion of subjects having less than 1 month of current episode. A BMI of >25 is considered as overweight, and both simple polypharmacy and complex polypharmacy groups had a significantly higher BMI than did the MS or AP monotherapy/polypharmacy group. The simple or complex polypharmacy group showed a significantly more overweight status than did the MS or AP monotherapy/polypharmacy group. The MS or AP monotherapy/polypharmacy

Table 1. Polypharmacy prescription patterns-related clinical characteristics in patients with bipolar disorder

	Total sample (N=348)	MS or AP monotherapy/ polypharmacy (N=51)	Simple polypharmacy (N=178)	Complex polypharmacy (N=119)	Statistical coefficients	p-value
Age, mean (SD) years	43.6 (15.2)	48.4 (17.7)	43.1 (15.0)	42.3 (14.0)	F=3.109	0.046
Female, N (%)	209 (60.1)	30 (58.8)	105 (59.0)	74 (62.2)	χ^2=0.342	0.843
Employed, N (%)	63 (18.1)	13 (25.5)	32 (18.0)	18 (15.1)	χ^2=2.590	0.274
Outpatient, N (%)	196 (56.3)	41 (80.4)	112 (62.0)	43 (36.1)	χ^2=34.876	<0.0001
Duration of illness, N (%)*					χ^2=8.279	0.602
<6 months	22 (6.7)	1 (2.2)	12 (7.2)	9 (7.9)		
6–12 months	6 (1.8)	0 (0.0)	3 (1.8)	3 (2.6)		
1–5 years	49 (15.0)	6 (13.3)	23 (13.8)	20 (17.5)		
5–10 years	75 (23.0)	10 (22.0)	46 (27.5)	19 (16.7)		
10–20 years	87 (26.7)	14 (31.1)	41 (24.6)	32 (28.1)		
>20 years	87 (26.7)	14 (31.1)	42 (25.1)	31 (27.2)		
Duration of untreated illness, N (%)†					χ^2=24.483	<0.0001
<6 months	115 (42.4)	14 (38.9)	70 (49.0)	31 (33.7)		
6–12 months	53 (19.6)	11 (30.6)	26 (18.2)	16 (17.4)		
1–5 years	68 (25.1)	4 (11.1)	26 (18.2)	38 (41.3)		
>5 years	35 (12.9)	7 (19.4)	21 (14.7)	7 (7.6)		
Polarity at onset, N (%)					χ^2=9.657	0.008
Depressive episode	78 (32.1)	15 (46.9)	42 (37.2)	21 (21.4)		
Manic episode	165 (67.9)	17 (53.1)	71 (62.8)	77 (78.6)		
Current episode, N (%)						
Depressive episode	36 (10.3)	10 (19.6)	19 (10.7)	7 (5.9)	χ^2=7.294	0.026
Manic episode	54 (15.5)	4 (7.8)	30 (16.9)	20 (16.8)	χ^2=2.685	0.261
Mixed episode	16 (4.6)	3 (5.9)	8 (4.5)	5 (4.2)	χ^2=0.239	0.887
Remission	215 (61.8)	30 (58.8)	104 (58.4)	81 (68.1)	χ^2=3.029	0.220
Duration of current episode, N (%)‡					χ^2=24.164	0.001
<1 month	77 (24.4)	4 (8.5)	33 (21.0)	40 (35.7)		
1–3 months	106 (33.5)	13 (27.7)	60 (38.2)	33 (29.5)		
3–6 months	40 (12.7)	9 (19.1)	19 (12.1)	12 (10.7)		
6–12 months	10 (6.0)	3 (6.4)	6 (3.8)	10 (8.9)		
>1 year	74 (23.4)	18 (38.3)	39 (24.8)	17 (15.2)		

Table 1. Polypharmacy prescription patterns-related clinical characteristics in patients with bipolar disorder (continued)

	Total sample (N=348)	MS or AP monotherapy/ polypharmacy (N=51)	Simple polypharmacy (N=178)	Complex polypharmacy (N=119)	Statistical coefficients	p-value
Rapid cycling in last 1 year, N (%)	6 (1.7)	0 (0.0)	3 (1.7)	3 (2.5)	χ^2=1.342	0.511
Rapid cycling in lifetime, N (%)	11 (3.2)	0 (0.0)	7 (3.9)	4 (3.4)	χ^2=2.027	0.363
Seasonality in last 1 year, N (%)	11 (3.2)	0 (0.0)	6 (3.4)	5 (4.2)	χ^2=2.111	0.348
Seasonality in lifetime, N (%)	11 (3.2)	0 (0.0)	7 (3.9)	4 (3.4)	χ^2=2.027	0.363
Body mass index, mean (SD) kg/m^2	24.3 (4.1)	22.7 (3.6)	24.6 (4.1)	24.6 (4.2)	F=4.767	0.009
Body mass index classification, N (%)					χ^2=18.364	0.012
Underweight	13 (3.7)	6 (11.8)	4 (2.2)	3 (2.5)		
Normal weight	201 (57.8)	34 (66.7)	99 (55.6)	68 (57.1)		
Overweight	103 (29.6)	9 (17.6)	59 (33.1)	35 (29.4)		
Obesity	31 (8.9)	2 (3.9)	16 (9.0)	13 (10.9)		
Antidepressant, N (%)	64 (18.4)	22 (34.4)	29 (16.3)	13 (10.9)	χ^2=25.752	< 0.0001
Anxiolytic, N (%)	167 (48.0)	25 (49.0)	71 (39.9)	71 (59.7)	χ^2=11.201	0.004
Hypnotic, N (%)	30 (8.6)	6 (11.8)	16 (9.0)	8 (6.7)	χ^2=1.215	0.545
Anti-parkinson, N (%)	45 (12.9)	3 (5.9)	22 (12.4)	20 (16.8)	χ^2=3.890	0.143

*N=328, †N=273, ‡N=318. AP: antipsychotic, MS: mood stabilizer, SD: standard deviation

group showed more use of antidepressants than did the other two groups. Even though 10.3% of subjects were in the currently depressive phase, only 52.8% of subjects with depressive phase were applied antidepressants. However, anxiolytic prescription was the most common in the complex polypharmacy group, followed by the MS or AP monotherapy/polypharmacy group and then the simple polypharmacy group. There was no significant difference in the proportion of sex, employment status, duration of BD, current episode (depressive episode, manic episode, mixed episode, and remission), history related to rapid cycling, feature related to seasonality and use of hypnotics, and anti-parkinsonian drug among subjects in the 3 discrete prescription groups.

DISCUSSION

From this study, tendency in simple or complex polypharmacy showed characteristics with younger age, higher inpatient proportion, larger portion of onset with depressive episode, shorter untreated illness, shorter duration of current episode, more overweight, less antidepressants use, and more anxiolytics use than simple polypharmacy.

Old age often makes subjects prone to side effects, an important factor considered when deciding upon prescriptions,[19] thus explaining why polypharmacy at a younger age may be more common.

Simple or complex polypharmacy, both represent types of combination therapy and may be preferred to MS or AP monotherapy in patients with severe BD, due to better efficacy, with approximately 20% more patients responding to combination therapy.[20,21] Subjects with inpatient settings can be interpreted as those having more severe symptoms. A shorter duration of untreated illness could represent a higher need for medical aid, suggesting a more serious clinical situation. A shorter duration of current illness also could be interpreted as need of quick treatment, which can be related to severe disability. In terms of long-term course, the onset of manic episode been associated with a higher number of hospitalizations, suicide attempts, and episodes with psychotic symptoms.[22,23] Moreover, comorbid anxiety is known to decrease the response to MSs, and as comorbid anxiety disorder or distress is often reported in BD patients, this may be a cause for increasing polypharmacy.[24,25] Antidepressant use in our study had different finding with previous report, which observed increased antidepressant prescription in subjects with polypharmacy, most frequently prescribed with escitalopram in subjects with comorbid anxiety.[26] Meanwhile, the fewer antidepressant prescriptions in the polypharmacy group in this study could be explained by the sedating effect of the antidepressant trazodone, which also can be explained by less frequent prescrip-

tion in depressive subjects. More subjects with overweight in polypharmacy group was in line with recent report, which showed association with BD state and elevated BMI both impact hippocampal concentration of neurochemicals relevant to BD.[27] Careful interpretation on overweight observed in polypharmacy subjects is needed because our study has a cross-sectional design, and results are difficult to be explained by causality. However, it is common for patients with BD to be overweight or obese, which requires regular monitoring on weight changes.[28,29]

This study had several limitations. First, the REAP-BD is not a typical epidemiological survey, therefore it needs careful interpretation when generalizing. Second, the application of objective scales for clinical evaluation and psychiatric comorbidity were not assessed, meaning there was a lack of an overview of functional status. Third, despite the involvement in conferences, variations in clinical evaluation often occur between different researchers.

However, even with these limitations, we showed a high proportion of polypharmacy in BD from the Korean data of the REAP-BD study and discussed clinical characteristics associated with polypharmacy. These clinical characteristics suggest a more severe state of BD are associated with polypharmacy, findings which could offer further perspectives for future research tailored for individual state.[30]

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Park S-C, Lin S-K, Tan CH, Shinfuku N, Park YC. Data curation: Park S-C, Kim K, Yang H, Na E, Lee H, Jang O-J, Yoon H-J, Oh HS, Ham B-J, Park YC. Funding acquisition: Park S-C. Investigation: Park S-C, Kim K, Yang H, Na E, Lee H, Jang O-J, Yoon H-J, Oh HS, Ham B-J, Park YC. Methodology: Park S-C, Lin S-K, Tan CH, Shinfuku N, Park YC. Project administration: Park S-C, Lin S-K, Tan CH, Shinfuku N, Park YC. Supervision: Lin S-K, Tan CH, Shinfuku N, Park YC. Writing—original draft: Kim K. Writing— review & editing: Kim K, Park S-C, Park YC.

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