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The Dropout Rates and Associated Factors in Patients with Mood Disorders in Long-term Naturalistic Treatment

Wooyoung Jung[1], Eunsoo Moon[2,3], Hyun Ju Lim[2], Je Min Park[2,3], Byung Dae Lee[2,3], Young Min Lee[2,3], Heejeong Jeong[2], Hwagyu Suh[2], Kyungwon Kim[2]

[1]Jung Wooyoung Psychiatry Clinic, Busan, Korea
[2]Department of Psychiatry and Biomedical Research Institute, Pusan National University Hospital, Busan, Korea
[3]Department of Psychiatry, Pusan National University School of Medicine, Yangsan, Korea

Objective: Although maintenance treatment for mood disorders is important, the treatment discontinuation rate is reported to be high. This study aimed to investigate the dropout rates and associated factors in mood disorders.
Methods: The patients in a mood disorder clinic (n = 535) were examined. Demographic and clinical factors, scores of psychometric scales, time to dropout from initial treatment in patients with bipolar disorder (BP) (n = 288) and depressive disorder (DD) (n = 143) were evaluated based on database of the mood disorder clinic.
Results: Among the studied patients with BP and DD, 50% showed dropout in 4.05 and 2.17 years, respectively. The mean survival times were 8.90 years in bipolar disorder I (BP-I), 5.19 years in bipolar II disorder, 3.22 years in bipolar disorder not otherwise specified, 4.24 years in major depressive disorder, and 4.03 years in other depressive disorders. In the multivariate Cox proportional hazards regression model in the BP group, diagnosis BP-I was found to be significantly related to the decrease in dropout rate (hazard ratio [HR] = 0.22, p = 0.001); however, increased past suicide attempt number was significantly related to the increase in dropout rate (HR = 1.13, p = 0.017). In the DD group, none of anxiety disorders as comorbidity, increased scores of openness, and extraversion personality were related to the increase in dropout rate.
Conclusion: Patients with BP, especially BP-I, showed a lower dropout rate as compared to patients with other mood disorders.

KEY WORDS: Bipolar disorder; Depressive disorder; Affect; Treatment adherence.

INTRODUCTION

Bipolar disorder (BP) is a chronic and relapsing psychiatric illness that features various episodes of mania, depressive, mixed state, or euthymic states. The maintenance of mood stability and assurance of best functioning are the primary purpose of treatment in BP [1,2], as shorter durations of euthymic states between relapses are associated with poorer functioning, higher odds of suicidality, unemployment and hospitalization [3,4]. Therefore, when mood stability is accomplished from acute management, the next important goal is to maintain recovery and prevent relapse of the illness in the maintenance phase [1]. About 10−15% of patients with BP have a severe and treatment-resistant traits [5]. However, more frequently, relapse in BP is caused by medication non-adherence. Accordingly, it is known that around 40% of patients with BP are non-adherent to their medication [6]. Furthermore, in a naturalistic follow-up study, 'Systematic Treatment Enhancement Program for Bipolar Disorder' (STEP-BD), 32% of all study participants did not complete their 1 year of treatment, and they were classified as dropped [7]. This evidence suggests that behavioral adherence could also be a principal factor for successful treatment in BP [8].

Major depressive disorder (MDD) is another common disabling psychiatric illness. Relapse and recurrence of MDD can be prevented by continuing antidepressant medi-

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Address for correspondence: Eunsoo Moon
Department of Psychiatry and Biomedical Research Institute, Pusan National University Hospital, Pusan National University School of Medicine, 179 Gudeok-ro, Seo-gu, Busan 49241, Korea
E-mail: esmun@hanmail.net
ORCID: https://orcid.org/0000-0002-8863-3413

cation [9,10]. Most treatment guidelines of MDD emphasize maintaining treatments and continuing antidepressant medication after symptom remission. For instance, according to the Canadian Network for Mood and Anxiety Treatment Clinical guidelines for treatment of MDD, patients should maintain antidepressant medication for at least 6−9 months after full symptom remission, while patients with some risk factors, such as recurrent episodes (≥ 3), psychotic episodes, chronic episodes, significant comorbidities, or difficult-to-treat episodes, should continue antidepressant medication for at least 2 years, and some may need even lifetime use [11]. However, despite the importance of treatment maintenance for depression, many patients discontinue antidepressant use earlier in the course of treatment. In previous research, approximately 31% of patients were found to have at least one 3-day drug holiday during 9 weeks [12]. About 28% of patients stop taking their antidepressant within 1 month and 44% within 3 months [13]. Such high early discontinuation rates are crucial difficulties for a successful treatment of MDD [14].

Overall, premature discontinuation of scheduled follow-up visits is a common problem in the treatment of chronic disorders such as schizophrenia and affective disorder, as well as in physical diseases such as diabetes mellitus and hypertension. Premature discontinuation of scheduled follow-up visits frequently results in an important medical and social burden. In several articles, such premature discontinuation of scheduled follow-up visits was referred to as "treatment-drop-out, non-attendance, missed appointment, no show" [15,16]. However, regardless of the definition, it has been suggested that the insufficient duration of treatment resulting from dropouts could increase the risk of recurrence, re-hospitalization, and psychosocial deficit [17,18], as dropout is an ultimate form of significant non-adherence that hampers patients from having assistance from professionals who can resume treatment as soon as symptoms begin to return [19]. Since the treatment maintenance has been emphasized in the management of chronic relapsing mood disorders, and considering that early dropout is a critical issue in successful management of mood disorders, it is meaningful to investigate dropout rates and find associated factors with dropout. In addition, taking into account that mood disorders have an episodic nature, a long-term observation for the subjects is necessary to get sufficient data about dropout.

However, most previous clinical studies on treatment maintenance and efficacy and safety of medication have focused on relatively short-term effects [20-22]. Moreover, conventional randomized trials may not reflect the real clinical situation in some aspects, as absolute inclusion and exclusion criteria or systematized randomization of patients does not occur in real clinical settings [9,23]. Therefore, it is meaningful to investigate dropout rate and its associated factors through data obtained from actual clinical situations over a longer period of time at a specialized mood clinic. Therefore, the first aim of the present study is to compare the dropout rate in patients with BP and depressive disorder (DD) in the same real clinical setting. The second goal is to explore the effect of the patient's clinical characteristics such as age, sex, diagnosis, treatment types, psychiatric comorbidities, past suicidality, depressive/manic symptoms, attention deficit hyperactivity disorder (ADHD) symptoms, impulsivity, personality traits, and substance abuse on dropout in real clinical treatment.

METHODS

Subjects

The data from a total of 535 patients who completed diagnostic evaluation questionnaire from April 2010 to March 2021 in a mood disorder clinic were investigated to calculate the total number of potentially relevant study participants. Demographic and clinical factors, scores of psychometric scales, time to dropout from initial treatment were retrospectively obtained from electronic medical and database of the specialized mood disorder clinic. Exclusion criteria were as follows: 1) patients with missing values in their clinical scales; 2) patients with difficulty in distinguishing them from schizophrenia, schizoaffective disorder and other psychotic disorder; 3) patients with significant neurological disorders; 4) patients with intellectual disability; 5) patients with severe medical illnesses affecting psychiatric outpatient care; and 6) patients whose treatment was terminated by their physician. Based on the data filtering, 431 patients were included in the final data sample. According to Diagnostic and Statistical Manual of Mental Disorders Forth edition (DSM-IV) criteria, the diagnoses of the patients retained in the sample were bipolar I disorder (BP-I) (n = 91), bipolar II disorder (BP-II) (n = 60), bipolar disorder not otherwise specified (BP-NOS)

(n = 137), MDD (n = 90), other depressive disorder including dysthymic disorder (Dys), depressive disorder not otherwise specified (DD-NOS) (n = 53) (Table 1). All patients were diagnosed their final mood disorders and comorbidity by mood disorders specialist psychiatrist according to the Structured Clinical Interview for DSM-IV. The present study was approved by the Institutional Review Board of Pusan National University Hospital (PNUH: 2106-032-104).

Methods

Definition of dropout

The time taken to dropout was calculated by reviewing medical records. The definition of dropout was the condition where a patient stopped his or her treatment for over 1 month without discussion or contact with the doctor, despite recommendations for treatment by a psychiatrist [19]. If these patients did not visit the clinic within 1 month, they were regarded as intending to dropout. Duration from the first visit date to the mood disorder clinic to last visit date was defined as time to dropout [16].

Demographic factors and clinical variables

Demographic and clinical factors, as well as the results of various scales, were investigated to find the factors that have influence on dropout rates in mood disorders. Demographic factors included sex, age at the time of the study, education, marital status, job, religion and social economic status. Clinical factors included past psychiatric treatments, age at first psychiatric treatment, past psychiatric admissions, the number of past psychiatric admissions and of previous suicide attempts, head injury, psychiatric family history, dropout at the present, duration of follow-up, the number of psychiatric comorbidity disorders, anxiety disorders, and other psychiatric disorders as comorbidities (panic disorder, social phobia, obsessive compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, eating disorders, alcohol abuse or alcohol dependence).

Clinical scales for assess mood symptom, temperament, and other associated factors

Mood Disorder Questionnaire (MDQ): The MDQ is a screening tool for BP that can easily be used in primary care settings. MDQ has both good sensitivity and specificity. It contains 13 questions plus items assessing clustering of symptoms and functional impairments [24,25].

Bipolar Spectrum Diagnostic Scale (BSDS): The BSDS is a bipolar spectrum screening scale and contains two

Table 1. Demographic factors of the patients with bipolar and depressive disorders

Variable	Bipolar disorders	Depressive disorders	p value
Sex (n = 431)			
Male	126 (43.8)	162 (56.3)	$\chi^2 < 1$, df = 1, $p = 0.950$
Female	63 (44.1)	80 (55.9)	
Age at the 1st evaluation	33.25 ± 12.17	42.32 ± 15.51	t = −6.12, df = 231.37, $p = 0.000$*
Education (yr) (n = 414)	13.94 ± 2.24	13.12 ± 2.97	t = 2.85, df = 212.62, $p = 0.005$*
Marital status (n = 422)			$\chi^2 = 16.39$, df = 2, $p = 0.000$*
Married	76 (27.0)	64 (45.4)	
Divorced, widowed, separation	34 (12.1)	19 (13.5)	
Unmarried	171 (60.9)	58 (41.1)	
Job (n = 415)			
None	77 (28.0)	32 (22.9)	$\chi^2 = 1.49$, df = 2, $p = 0.475$
Full time & part time	99 (36.0)	57 (40.7)	
Student & house wife	99 (36.0)	51 (36.4)	
SES (n = 321)			$\chi^2 = 0.77$, df = 4, $p = 0.943$
Very rich	6 (2.7)	4 (3.9)	
Good	46 (20.9)	24 (23.8)	
Relatively fair	79 (35.9)	35 (34.7)	
Poor	49 (22.3)	21 (20.8)	
Very poor	40 (18.2)	17 (16.8)	

Values are presented as number (%) or mean ± standard deviation.
SES, social economic status.
*$p < 0.05$.

parts. The first part begins with a short story by addressing the patient as the third person and contains 19 sentences, including the subtle symptoms of BP. In case a person can relate to a sentence, 1 point is given to him/her. The second part, which contains multiple-choice questions, is given to the person upon the appropriate score ranging from 0 to 6 [26].

Alcohol Use Disorders Identification Test (AUDIT): The AUDIT is a screening instrument for identification of hazardous alcohol use. The scale contains 10 items across three dimensions related to alcohol consumption, dependence symptoms, and harmful alcohol use [27].

Fagerstrom Test for Nicotine Dependence (FTND): The FTND is designed to assess nicotine dependence. It is a noninvasive and easy to acquire self-report instrument that conceptualizes dependence through physiological and behavioral symptoms [28].

Adult ADHD Self-Report Scale (ASRS): The ASRS is a symptom checklist tool including 18 ADHD symptoms from the DSM-IV criteria for children, which was modified for adult ADHD. The 18-question version was distributed into inattentive and hyperactive/impulsivity group of symptoms [29].

Multi-dimensional Scale of Perceived Social Support (MSPSS): The MSPSS is a brief 12-item, self-administered measurement instrument with three subscales: Family, Friends, and Significant Others. A higher score means a greater the social support perceived by an individual [30].

Temperament and Character Inventory (TCI-240): The TCI includes 240 items in four temperament dimensions: novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (P) and three character dimensions: self-directedness (SD), cooperativeness (C), self-transcendence (ST) [31].

Neuroticism-Extraversion-Openness Inventory (NEO-60): The NEO-60 inventory is s a multidimensional measure of normal personality traits to evaluate five major personality dimensions or domains: neuroticism (N), extraversion (E), openness (O), agreeableness (A), and conscientiousness (C) [32].

Barratt Impulsiveness Scale (BIS): The BIS-11 is a self-report questionnaire to estimate the trait impulsivity. BIS includes attentional, motor, and non-planning subscales. Motor impulsiveness is an indicator of behavioral impulsivity. Attentional impulsiveness and non-planning impulsiveness are supposed to be indicators of cognitive impulsiveness [33].

Statistics

A chi-square test for categorical variables and an independent t test for continuous variables were used to compare the differences of demographic and categorical variables between the BP and DD groups. The time taken to dropout in each mood disorder and in BP and DD was investigated using Kaplan–Meier survival analysis. The univariate and multivariate Cox proportional hazards regression model was applied to analyze factors that influence the time to dropout. SPSS 22.0 for Windows (IBM Co.) was used to analyze all data. All statistics were two-tailed, and significance level was set to $p < 0.05$.

RESULTS

Demographic Factors of the Subjects

The demographic factors of the subjects are summarized in Table 1. Age at the first evaluation in the BP group was significantly younger than that in the DD group (33.25 vs. 42.32 years old, $p = 0.000$). Duration of education of in the BP group was significantly longer than that in the DD group (13.94 vs. 13.12 years, $p = 0.005$). Marital status in the two groups was significantly different ($p = 0.000$), with 27.0% married patients in the BP group and 45.4% in the DD group. Sex, job, and social economic status were not significantly different in the two groups.

Clinical Variables of the Subjects

As shown in Table 2, percentage of the subjects without previous psychiatric treatment history (BP group 21.1% vs. DD group 43.3%, $p = 0.000$), and age at the first psychiatric treatment (27.87 vs. 38.66, $p = 0.000$) was significantly lower in the BP group as compared to the DD group. The rate of past psychiatric admission history (36.5% vs. 9.8%) and the rate of psychiatric family history (40.6% vs. 22.4%, $p = 0.000$) were significantly higher in the BP group than in the DD group. Duration of follow-up was significantly longer in the BP group than in the DD group (3.64 vs. 2.76, $p = 0.009$). The BP group had a significantly higher psychiatric comorbidity compared to the DD group (1.02 vs. 0.71, $p = 0.010$). Furthermore, the BP group had a significantly greater alcohol abuse or dependence as a comorbidity than the DD group (16.0 % vs. 3.8%, $p = 0.000$). Total score of AUDIT (7.89 vs. 4.83, $p =$

Table 2. Clinical variables of the patients with bipolar and depressive disorders

Variable	Bipolar disorders	Depressive disorders	*p* value
Past NP treatment (n = 426)			χ^2 = 23.92, df = 2, *p* = 0.000*
None	60 (21.1)	61 (43.3)	
Irregular	105 (36.8)	43 (30.5)	
Regular	120 (42.1)	37 (26.2)	
Age at 1st NP treatment (n = 431)	27.87 ± 11.07	38.66 ± 15.74	t = −7.35, df = 213.96, *p* = 0.000*
Past NP admission (n = 431)			χ^2 = 34.00, df = 1, *p* = 0.000*
No	183 (63.5)	129 (90.2)	
yes	105 (36.5)	14 (9.8)	
The number of previous suicide attempt (n = 427)	0.85 ± 2.10	0.80 ± 0.80	t = 0.182, df = 43, *p* = 0.855
NP family history (n = 431)			χ^2 = 16.05, df = 2, *p* = 0.000*
No	168 (58.3)	106 (74.1)	
yes	117 (40.6)	32 (22.4)	
Clinical diagnosis (n = 431)			
Bipolar I disorder	91 (31.6)		
Bipolar II disorder	60 (20.8)		
Bipolar disorder NOS	137 (47.6)		
Major depressive disorder		90 (62.9)	
Dysthymia or depressive disorder NOS		53 (37.1)	
Dropout or follow-up (n = 431)			χ^2 = 3.48, df = 1, *p* = 0.062
Dropout	175 (60.8)	100 (69.9)	
Follow-up	113 (39.2)	43 (30.1)	
Duration of follow-up (yr) (n = 431)	3.64 ± 3.80	2.76 ± 2.98	t = 2.64, df = 350.47, *p* = 0.009*
The number of psychiatric comorbidity disorders (n = 430)	1.02 ± 1.24	0.71 ± 1.04	t = 2.58, df = 428, *p* = 0.010*
Comorbidity-any anxiety disorder (n = 430)			χ^2 = 2.19, df = 1, *p* = 0.139
No	153 (53.3)	87 (60.8)	
Yes	134 (46.7)	56 (39.2)	
Comorbidity-eating disorders (n = 428)			χ^2 = 3.63, df = 1, *p* = 0.057
No	267 (93.7)	140 (97.9)	
Yes	18 (6.3)	3 (2.1)	
Comorbidity-alcohol abuse or alcohol dependence (n = 430)			χ^2 = 16.26, df = 1, *p* = 0.000*
No	241 (84.0)	139 (97.2)	
Yes	46 (16.0)	4 (3.8)	
BDI (n = 395)			
Total	25.22 ± 14.24	25.69 ± 14.24	t = −0.32., df = 393, *p* = 0.751
Total MDQ (n = 387)	8.71 ± 3.34	4.38 ± 3.25	t = 12.10, df = 385, *p* = 0.000*
BSDS (n = 427)			
Total	10.45 ± 6.88	6.80 ± 12.35	t = 3.91, df = 425, *p* = 0.000*
Depressive	4.79 ± 2.91	2.83 ± 2.37	t = 6.41, df = 367, *p* = 0.000*
Manic	3.522 ± 3.00	1.050 ± 1.69	t = 10.09, df= 357.57, *p* = 0.000*
AUDIT total (n = 368)	7.89 ± 8.95	4.83 ± 6.47	t = 3.75, df = 317.96, *p* = 0.000*
FTND total (n = 346)	1.60 ± 2.54	1.03 ± 2.12	t = 2.22, df = 279.10, *p* = 0.028*
ASRS (n = 291)			
Inattention	16.36 ± 7.23	13.34 ± 7.3	t = 3.21, df = 289, *p* = 0.001*
Hyperactivity-impulsivity	12.52 ± 7.11	9.22 ± 5.86	t = 4.07, df = 181.73, *p* = 0.000*
Total	28.88 ± 13.25	22.55 ± 12.15	t = 3.76, df = 289, *p* = 0.000*
MSPSS (n = 315)			
Family	18.40 ± 7.39	18.43 ± 6.88	t = −0.37, df = 313, *p* = 0.971
Friend	14.86 ± 8.01	14.67 ± 7.31	t = 0.20, df = 313, *p* = 0.843
Significant other	17.82 ± 7.97	17.45 ± 6.94	t = 0.42, df = 212.56, *p* = 0.674
Total	50.34 ± 20.84	50.55 ± 16.66	t = −0.10, df = 229.84, *p* = 0.922
TCI (n = 300)			
Novelty seeking	18.91 ± 6.151	16.12 ± 6.209	t = 3.634, df= 295, *p* = 0.000*
Harm avoidance	23.38 ± 7.633	24.65 ± 6.016	t = −1.555, df = 224.789, *p* = 0.121
Reward dependence	14.32 ± 3.986	14.17 ± 4.270	t = 0.286, df= 298, *p* = 0.775
Persistence	4.33 ± 2.048	4.03 ± 2.241	t = 1.154, df= 298, *p* = 0.249
Self directedness	20.08 ± 9.151	21.28 ± 8.493	t = −1.076, df = 298, *p* = 0.283
Cooperativeness	26.05 ± 7.233	26.67 ± 7.554	t = −0.681, df= 298, *p* = 0.496
Self transcendence	12.41 ± 7.035	8.51 ± 5.419	t = 5.249, df = 229.459, *p* = 0.000*

Table 2. Continued

Variable	Bipolar disorders	Depressive disorders	*p* value
NEO (n = 298)			
Neuroticism	42.84 ± 9.047	43.29 ± 7.762	t = −0.416, df = 296, $p = 0.677$
Extraversion	33.63 ± 8.549	32.09 ± 8.587	t = 1.442, df= 296, $p = 0.150$
Openness	38.92 ± 6.456	34.96 ± 5.793	t = 5.068, df= 296, $p = 0.000$
Agreeableness	39.60 ± 5.486	40.35 ± 5.604	t = −1.100, df = 296, $p = 0.272$
Conscientiousness	37.72 ± 7.484	38.73 ± 7.635	t = −1.077, df = 296, $p = 0.282$
BIS (n = 303)			
Cognitive	17.49 ± 3.893	16.93 ± 3.452	t = 1.204, df= 301, $p = 0.230$
Motor	22.71 ± 5.223	21.04 ± 5.056	t = 2.600, df= 301, $p = 0.010$
Non planning	28.37 ± 5.064	28.66 ± 5.146	t = −0.461, df = 301, $p = 0.645$
Total impulsiveness	68.57 ± 11.959	66.63 ± 11.602	t = 1.319, df = 301, $p = 0.188$

Values are presented as number (%) or mean ± standard deviation.
NP, neuropsychiatry; NOS, not otherwise specified; BDI, Beck Depression Inventory; MDQ, Mood Disorder Questionnaire; BSDS, Bipolar Spectrum Diagnostic Scale; MSPSS, Multidimensional Scale of Perceived Social Support; AUDIT, Alcohol Use Disorders Identification Test; FTND, Fagerstrom Test for Nicotine Dependence; ASRS, Adult ADHD Self-Report Scale; TCI, Temperament and Character Inventory; NEO, neuroticism-extraversion-openness inventory; BIS, Barratt Impulsiveness Scale.
*$p < 0.05$.

0.000) and FTND (1.60 vs. 1.03, $p = 0.028$) were significantly higher in the BP group than in the DD group. Total score of MDQ in the BP group was significantly higher than those in the DD group (8.71 vs. 4.38, $p = 0.000$). Total score (10.45 vs. 6.80, $p = 0.000$), depressive (4.79 vs. 2.83, $p = 0.000$) and manic (3.52 vs. 1.05, $p = 0.000$) scores of BSDS in the BP group were also significantly higher than those in the DD group. Total score (28.88 vs. 22.55, $p = 0.000$), inattention (16.36 vs. 13.34, $p = 0.001$) and hyperactivity-impulsivity score (12.52 vs. 9.22, $p = 0.000$) of ASRS were significantly higher in the BP group as compared to the DD group. In TCI, the score of NS and ST were higher in the BP group than in the DD group (NS: 18.91 vs. 16.12, $p = 0.000$ / ST: 12.41 vs. 8.51, $p = 0.000$).

The number of previous suicide attempts, percentage of dropout, the number of subjects having any anxiety disorder as comorbidity and eating disorder were not significantly different between the two groups. Total score of BDI, MSPSS, TCI (except for NS and ST), NEO and BIS were not significantly different between the two groups.

Dropout Rates of BP and DD

Comparing between BP and DD, 25% of the patients with BP dropped out in 0.52 year after the first visit. Furthermore, 50% and 75% of the patients with BP dropped out in 4.05 and 9.84 years, respectively. In the case of patients with DD, 25% of patients dropped out in 0.36 year after the first visit. In addition, 50% and 75% of the patients with DD dropped out in 2.17 and 7.45 years, respectively (Fig. 1A). Mean survival time was 5.82 years in BP and 4.18 years in DD.

Comparing individual mood disorders involved in BP and DD, 25% and 50% of the patients with BP-I dropped out in 2.89 and 9.63 years, respectively. However, 36.6% of the patients with BP-I did not drop out before 14.75 years. In addition, 25%, 50%, and 75% of the patients with BP-II dropped out in 0.93, 1.21 and 7.55 years, respectively. Likewise, 25%, 50%, and 75% of the patients with BP-NOS dropped out in 0.19, 1.65 and 5.33 years, respectively. In addition, 25%, 50%, and 75% of the patients with MDD dropped out in 0.35, 2.57 and 7.63 years, respectively. Furthermore, 25%, 50%, and 75% of the patients with other depressive disorders (DD-NOS, Dys) dropped out in 0.36, 1.98, and 6.94 years, respectively (Fig. 1B). Mean survival time was 8.90 years in BP-I, 5.19 years in BP-II, 3.22 years in BP-NOS, 4.24 years in MDD, and 4.03 years in patients with other depressive disorders.

Associated Factors to Dropout Rates

In the univariate Cox proportional hazards regression model in the BP group (Table 3), the patients treated in the outpatient clinic showed a significant increase in dropout risk (HR = 2.36, $p = 0.000$). The lack of past psychiatric treatment history in outpatient (HR = 1.94, $p = 0.000$) or admission (HR = 2.05, $p = 0.000$) was significantly related to the increase in the dropout rate. A higher number of

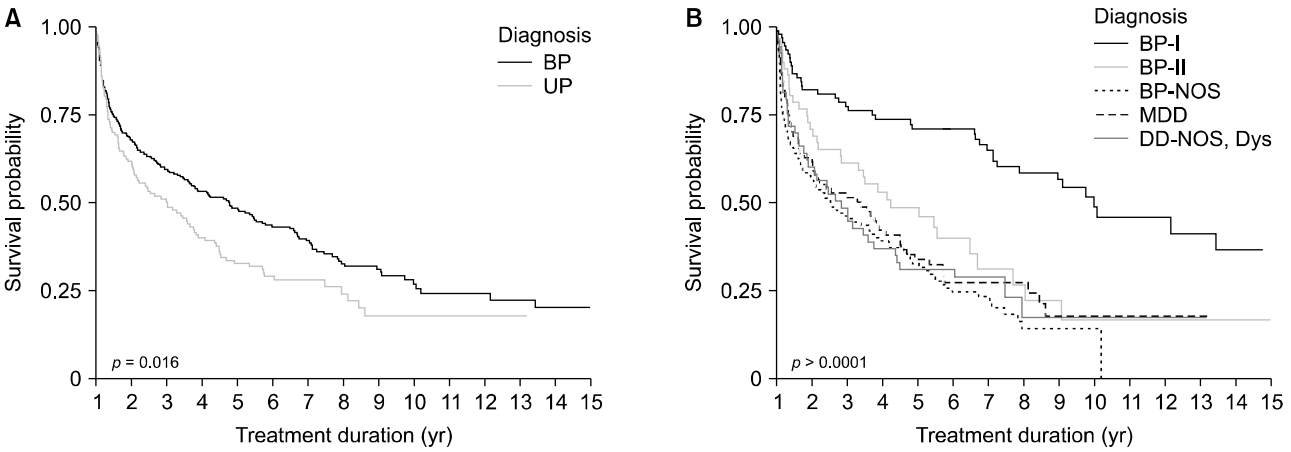

Fig. 1. (A) Survival plot ot time to dropout using the Kaplan–Meier method for patients with bipolar and depressive disorder. Overall, 25% of the patients with BP dropped out in 0.52 year after the first visit; 50% percent and 75% of the patients with BP dropped out in 4.05 and 9.84 years, respectively; 25% of the patients with DD droppedout in 0.36 year after the first visit; finally, 50% and 75% of the patients with DD dropped out in 2.17 and 7.45 years, respectively. (B) Survival plot ot time to dropout using the Kaplan–Meier method for patients with each mood disorders. Overall, the dropout rates for different mood disorders varied. For patients with BP-I, 25% dropped out within 2.89 years, while 50% dropped out within 9.63 years, and notably 36.6% remained until 14.75 years. As for BP-II, 25% dropped out in 0.93 years, 50% in 1.21 years, and 75% in 7.55 years. Patients with BP-NOS had 25%, 50%, and 75% dropout rates within 0.19, 1.65, and 5.33 years, respectively. Meanwhile, 25%, 50%, and 75% of the MDD patients, the dropout rates were 0.35, 2.57, and 7.63 years. Lastly, DD-NOS showed 25%, 50%, and 75% dropout rates within 0.36, 1.98, and 6.94 years, respectively.
BP, bipolar disorders; UP, unipolar disorders; BP-I, bipolar I disorder; BP-II, bipolar II disorder; BP-NOS, bipolar disorder not other specified; MDD, major depressive disorder; DD-NOS, depressive disorder not otherwise specified; Dys, dysthymic disorder.

Table 3. Analysis of the factors affecting the time to dropout through a Cox proportional hazards regression model in the patients with bipolar disorders

Variable	Reference	B	S.E.	Wald's χ^2	df	p value	Hazard ratio	95% CI of hazard ratio
Bipolar disorders univariate (n = 288)								
OPD or ADM	OPD	0.86	0.23	14.50	1	0.000	2.36	1.52−3.66
Diagnosis	BP-I	−1.22	0.20	38.93	1	0.000	0.30	0.20−0.43
	BP-II	−0.43	0.20	4.81	1	0.028	0.65	0.44−0.96
Age at 1st NP treatment		−0.02	0.01	8.15	1	0.004	0.98	0.97−0.99
Past NP TX_OPD	NONE	0.66	0.17	14.87	1	0.000	1.94	1.39−2.72
Past NP TX_ADM	NONE	0.72	0.17	17.97	1	0.000	2.05	1.47−2.85
1st NP admission age		−0.02	0.01	9.50	1	0.002	0.98	0.97−0.99
Past suicide number		0.10	0.03	9.92	1	0.002	1.11	1.04−1.18
BDI-total		0.01	0.01	6.60	1	0.010	1.02	1.01−1.03
BSDS-total		0.02	0.01	5.09	1	0.024	1.02	1.01−1.05
ASRS-hyperactivitiy-impulsivity		0.04	0.01	10.25	1	0.001	1.04	1.02−1.07
ASRS-total		0.02	0.01	7.94	1	0.005	1.02	1.01−1.04
TCI self directedness		−0.04	0.01	11.59	1	0.001	0.96	0.94−0.98
NEO agreeableness		−0.04	0.02	5.04	1	0.025	0.96	0.93−0.99
BIS motor		0.04	0.02	3.91	1	0.048	1.04	1.00−1.07
BIS total impulsiveness		0.02	0.01	4.43	1	0.035	1.02	1.00−1.03
Muti-variate								
Diagnosis	BP-I	−1.51	0.47	10.46	1	0.001	0.22	0.09−0.55
Past suicide number		0.12	0.05	5.66	1	0.017	1.13	1.02−1.24

S.E., standard error; BP-I, bipolar I disorder; BP-II, bipolar II disorder; NP, neuropsychiatry; OPD, outpatient psychiatric clinic; TX, treatment; ADM, admission to psychiatric closed ward; BDI, Beck Depression Inventory; BSDS, Bipolar Spectrum Diagnostic Scale; ASRS, Adult ADHD Self-Report Scale; TCI, Temperament and Character Inventory; NEO, neuroticism-extraversion-openness inventory; BIS, Barratt Impulsiveness Scale; CI, confidence interval.

Table 4. Analysis of the factors affecting the time to dropout through a Cox proportional hazards regression model in the patients with depressive disorders

Variable	B	S.E.	Wald's χ^2	df	p value	Hazard ratio	95% CI of hazard ratio
Depressive disorders univariate (n = 143)							
Comorbidity number	−0.38	0.13	9.13	1	0.003	0.68	0.53−0.87
No anxiety dis	0.80	0.23	12.40	1	0.000	2.22	1.42−3.45
TCI-self directedness	−0.04	0.02	4.53	1	0.033	0.97	0.93−0.99
NEO extraversion	0.04	0.02	5.29	1	0.021	1.04	1.01−1.08
NEO openness	0.06	0.02	5.46	1	0.020	1.06	1.01−1.11
Multi-variate (n = 143)							
No anxiety dis	1.07	0.49	4.85	1	0.028	2.91	1.12−7.52
TCI-self directedness	−0.06	0.02	11.78	1	0.001	0.94	0.91−0.97
NEO_openness_60	0.07	0.02	7.96	1	0.005	1.07	1.02−1.12
NEO_extraversion	0.05	0.02	6.13	1	0.013	1.05	1.01−1.10

S.E., standard error; TCI, Temperament and Character Inventory; NEO, neuroticism-extraversion-openness inventory; CI, confidence interval.

past suicides (HR = 1.11, p = 0.002), increased score of BDI (HR = 1.02, p = 0.010) and BSDS (HR = 1.02, p = 0.024), increased hyperactive-impulsivity and a total score in ASRS (HR = 1.02, p = 0.005), an increased score of motor (HR = 1.04, p = 0.048) and total impulsiveness (HR = 1.02, p = 0.035) in BIS were significantly related to increase in dropout rate. In contrast, diagnosis of BP-I (HR = 0.30, p = 0.000) and BP-II (HR = 0.65, p = 0.028), increased age of first psychiatric treatment (HR = 0.98, p = 0.004) and first neuropsychiatry (NP) admission age (HR = 0.98, p = 0.002), increased scores of self-directedness in TCI (HR = 0.96, p = 0.001), and agreeableness in NEO (HR = 0.96, p = 0.025) were significantly related to a decrease in dropout rate. In the multivariate Cox proportional hazards regression model in the BP group, diagnosis BP-I was significantly related to decrease in dropout rate (HR = 0.22, p = 0.001); however, increased past suicide attempt numbers was significantly related to an increase in dropout rate (HR = 1.13, p = 0.017).

In the univariate Cox proportional hazards regression model in the DD group (Table 4), none of anxiety disorders as a comorbidity, increased scores of extraversion, and openness in NEO was significantly related to an increase in dropout rate. In contrast, increased total comorbidity number and self-directedness in TCI were significantly related to a decrease in dropout rate. In the multivariate Cox proportional hazards regression model in the DD group, none of anxiety disorders as a comorbidity, increased scores of openness, and extraversion in NEO was related to an increase in dropout rate.

DISCUSSION

In the present study, the dropout rate of BP after 1 year and 3 years amounted to 37.5% and 55.2%, respectively. The dropout rate of BP was similar to the findings reported the previous studies. For example, in another Korean study including 275 patients with BP-I or BP-II, the treatment discontinuation rate for 1 year and 3 years were 33.8% and 50.2%, respectively [16]. Mazza *et al.* [34] reported treatment dropout of BP for 1 year of 38%. The dropout rate of DD after 1 year and 3 years in this study was 43.4% and 62.9%, respectively. Compared to previous studies, it seems to be relatively lower. Jung *et al.* [9] reported that 73% of patients with MDD discontinued antidepressant treatment after 24 weeks. Furthermore, Demyttenaere *et al.* [35] reported that 53% of patients with MDD discontinued antidepressant treatment after 6 months. However, due to the differences in the studied samples, it is difficult to directly compare the results of this study and the findings of previous studies. For example, as compared to the subjects of Jung *et al.*'s study [9], subjects in this study had a more history of psychiatric treatment.

The patients with BP showed a longer duration of follow-up as compared to the patients with DD. In particular, the patients with BP-I showed a longer duration of follow-up as compared to the patients with other BP and DD. Therefore, a significantly longer follow-up period in BP-I appears to affect the difference between two groups of mood disorders. Patients with bipolar disorder may have a high initial dropout rate due to the lack of insight. García *et al.* [36] reported that poor insight was one of the

main risk factors for medication non-adherence in bipolar disorder. However, since bipolar disorder is a serious disease, after several serious relapses, patients and their families may gradually establish insights for their psychiatric illness and maintain treatment. De Assis da Silva *et al.* [37] reported that a shorter illness duration was associated with lower levels of insight in mania. Considering that patients with BP in this study had more history of psychiatric admission or treatment, earlier first NP admission age, more NP family history and psychiatric comorbidity, they could have gotten psychoeducation more frequently and may have experienced more distress from their mood disorders. These factors may have influenced their attitudes and insights about the treatment. Higher early discontinuation rate of medication in DD may mean the lack of patients' conviction that the medication should be maintained, or some reasons that they cannot continue medication. Nonadherence is a multi-factorial phenomenon containing patient-related factors (e.g., misperceptions about antidepressant, adverse effects, lack of tolerability), physician-related factors (e.g., insufficient education from clinicians about depression and medication, lack of shared decision-making, poor follow-up care), and structural factors (e.g., access, cost, and stigma for psychiatry) [38,39]. Therefore, a careful observation for adherence and instruction for antidepressant medication are needed.

Meanwhile, 25% of the patients with DD maintained medication even in 7.45 years. This indicates that they may be a group with treatment resistant depression (TRD). In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the cumulative remission rate after 4 trials of antidepressants was 67% [40]. Even after sequential trials, from 10% to 20% of patients with MDD showed continuation of significant symptoms for 2 years or longer [41]. The patients with TRD continuously experienced depressive symptoms. This is related to a poorer outcome and, if symptoms do not remit, a higher psychiatric hospitalization rate, their functional impairment and risk of suicide can increase [42,43]. Maintenance of antidepressants after symptomatic remission has been recommended in most clinical practice guidelines. The majority recommended 6months, although some guidelines suggested longer periods depending on the specific clinical situation and the course of the illness [44]. However, well-organized clinical practice guidelines for patients with TRD are rare. Considering the heterogeneity of course of depression, and in view of the results of the present study and the difficulty of managing patients with TRD, a more systematized treatment and better management guidelines for patients with TRD reflecting real clinical situation are needed.

In BP, the dropout patients were likely to take outpatient treatment without admission in this follow-up period, show younger age of a first NP treatment and a first NP admission, and they did not have past NP treatment history. Furthermore, these groups showed even more suicide attempt history and had more depressive, manic symptoms at evaluation. Considering the results of ASRS and BIS in relation to dropout in BP, dropout seems to be related to some traits and characteristics such as increased impulsivity and ADHD-related symptoms. Fornaro *et al.* [15] also reported that a dropout case in BP endorsed a younger age at visit 1, earlier onset of depression. The results of the present study suggest that there is a group with a younger onset BP and a longer duration of illness, but not actively treated or with a lower compliance with the treatment because they may have not developed a good insight about the illness and awareness about their need for enduring care. In previous research, the impulsivity and ADHD-related symptoms were mentioned among the factors related to important trait, severity, course of illness in BP. Patients with BP may show increased levels of impulsivity even during remission periods. It is known that this dimensional trait has a negative impact on the course of disorder and deteriorate their prognosis [45]. Jiménez *et al.* [46] reported that impulsivity, as well as depressive symptoms and the number of hospitalizations, is associated with the overall functional impairment in BP, arguing that the assessment and treatment of impulsivity may be useful in improving functional outcome in BP. Perugi *et al.* [47] reported that, as compared to BP patients without adult ADHD, those with BP and adult ADHD have a higher rate of mixed states, more severe psychopathology, more impaired familial functioning, as well as higher rates of comorbid substance and alcohol and polydrug abuse.

Lower numbers of comorbidity, in particular, of anxiety disorders, were related to an increase dropout risk in patients with DD in the present study. Generally, a psychiatric comorbidity has been known to affect prognosis in both untreated and treated patients. Previous studies established that elevated baseline anxiety symptoms or comorbid anxiety disorders are related to worse antidepres-

sant response to first-line selective serotonin reuptake inhibitors (SSRIs) or second-line treatment strategies [48]. Anxiety subsequently contributes to increased severity and treatment resistance in patients with MDD [49]. In the present study, comorbid psychiatric illness in a particular anxiety disorder appeared to increase the likelihood of maintaining treatment in DD. Although comorbid psychiatric disorder may have a negative effect on treatment, patients with high anxiety may have a positive effect on their insight for mental illness and treatment adherence after experiencing chronic depression. For instance, in Hung *et al.*'s study [50], patients with chronic depression, panic/agoraphobia, or posttraumatic stress disorder as a comorbidity attended follow-up longer before discontinuation than those without.

In terms of the relation between personality factors and dropout, the dropout cases in BP showed a lower score of self-directedness and agreeableness. A lower score of self-directedness, a higher score extraversion and openness in NEO indicated a higher dropout risk in the DD group. Previous research highlighted an association with personality factors and mood disorders. Generally, people with low scores for SD are distinguished by a sense of inferiority, lack of initiative, proneness to wishful thinking, and blaming others for their mistakes. These traits are very similar to the representation of the depressive person, so it is probable that low SD scores are associated with occurrence of depression. Such findings emphasize that the patients with lower SD are less able to effectively and successfully deal with difficult life situations or adapt accordingly and apply their defense mechanisms to handle stressful situations [51-54]. In relation to patient characteristics, Zaninotto *et al.* [55] reported that patients with BP-1 only exhibited high self-transcendence, having a near normal profile in terms of harm avoidance or self-directedness. However, MDD and BP-II were characterized by high harm avoidance and low self-directedness [55]. In another previous research, patients with MDD showed lower score on extraversion than controls. In addition, the presence of depression and depression severity were connected to a lower score of extraversion. Relatively, openness is known to be the most disagreed upon factor, as there is no consensus in the literature on the extent to which openness is related to depression. Recently, Nikolic *et al.* [56] reported that MDD groups showed lower scores on openness and extraversion compared to healthy control groups. Although further research is needed to get conclusive findings, the difference of traits in these mood disorders may influence the attitude for treatment considering the results of the present study. In addition, evaluation of the patients' personality characteristics may be important to manage patients with mood disorders, because personality characteristics affect not only the development of the mental illness, but also the course of treatment.

The present study has several limitations. First, this study was a retrospective study and did not include various factors related to dropout. A further prospective study including various causes of dropout, such as medication adherence, hospital/costs, medical use issues, and personal factors should be performed to analyze the factors associated with dropout in real clinical setting. Second, this study used only self-rating scales. Further studies need to include clinician-assessed scales to compensate for the bias on the self-rating scales. Third, potential confounding factors affecting the dropout were not investigated and controlled, because this study was a retrospective study. In order to confirm the effect of the factors investigated in this study on dropout, it is necessary to investigate and control various confounding factors that can affect dropout in further studies. Fourth, specific treatment methods such as medications prescribed and psychosocial approach were not considered. Fifth, since patients' clinical courses and severities may differ considerably, the absence of an investigation for the number and character of mood episode especially in BP could be another limitation. Sixth, all subjects were the patients who visited inpatient or outpatient psychiatric clinic in only one hospital. Despite these limitations, this study investigated long-term clinical data of mood disorders including both BP and DD in real clinical settings, thus reflecting real clinical courses of patients diagnosed with mood disorders and treated in a psychiatric clinic.

In conclusion, patients with BP (and especially BP-I) showed a lower dropout rate as compared to patients with other mood disorders. Several clinical factors and personality factors were found to be related to increase dropout rate in mood disorders. As this study was conducted in one hospital retrospectively, further prospective study with a larger number of patients in multiple psychiatric clinics with a consideration of the result of this study will be necessary in order to better understand the protective and risk factors related to dropout in maintenance treatment.

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■ **Conflicts of Interest**

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

■ **Author Contributions**

Conception and design of the study: Wooyoung Jung, Eunsoo Moon. Acquisition of data: Wooyoung Jung, Eunsoo Moon, Hyun Ju Lim, Je Min Park, Byung Dae Lee, Young Min Lee, Heejeong Jeong, Hwagyu Suh, Kyungwon Kim. Analysis of data: Wooyoung Jung, Hyun Ju Lim. Writing−original draft: Wooyoung Jung. Writing−editing: Wooyoung Jung, Eunsoo Moon. Supervision: Eunsoo Moon. All authors reviewed the manuscript and approved it for submission.

■ **ORCID**

Wooyoung Jung	https://orcid.org/0000-0001-5844-7890
Eunsoo Moon	https://orcid.org/0000-0002-8863-3413
Hyun Ju Lim	https://orcid.org/0000-0002-8962-8173
Je Min Park	https://orcid.org/0000-0003-4700-5856
Byung Dae Lee	https://orcid.org/0000-0003-4295-8463
Young Min Lee	https://orcid.org/0000-0001-7483-7143
Heejeong Jeong	https://orcid.org/0000-0003-2833-1648
Hwagyu Suh	https://orcid.org/0000-0002-0360-6708
Kyungwon Kim	https://orcid.org/0000-0001-8947-9078

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