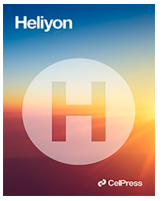
Heliyon 9 (2023) e20917

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Characteristics of persistent depression in the long-term: Randomized controlled trial and two-year observational study

Yosuke Koshikawa [a], Ai Onohara [b], Masataka Wakeno [a], Yoshiteru Takekita [a], Toshihiko Kinoshita [a], Masaki Kato [a,*]

[a] Department of Neuropsychiatry, Kansai Medical University, Osaka, Japan
[b] Social Welfare Corporation Uminoko Gakuen Ikejimaryo, Osaka, Japan

ARTICLE INFO

Keywords:
Persistent depressive disorder
Work and activities
General somatic symptoms
Insight
change the diagnosis to bipolar
major depressive disorder

ABSTRACT

Major depressive disorder is a chronic condition that can recur and relapse. It would be clinically useful to know the patient background to predict the chronicity of depressive symptoms, and the change in diagnosis of bipolar disorder. This study included 197 patients enrolled in a six-week randomized controlled trial with a two-year follow-up. We conducted multiple logistic regression analyses to identify the clinical and sociodemographic characteristics associated with persistent depressive disorder (PDD), relapse, and changes in bipolar disorder diagnosis. The significantly correlated factors were residual symptoms, including insight, work and activity, and general somatic symptoms at week six. We could not identify any factors that contributed to relapse or change in the diagnosis of bipolar disorder. We found that the specific residual symptoms of acute treatment affected long-term treatment outcomes for depression. Attention should be paid to the residual symptoms of depression in the early stages of treatment, and measures should be considered to improve them. There are several limitations to this study, including the fact that PDD may exist among patients who discontinued treatment, treatment was not standardized during the study period, and adherence was confirmed verbally.

1. Introduction

Major depressive disorder (MDD) is a chronic condition that can recur or relapse. It has been reported that about 28.2 % of depressed patients develop persistent symptoms [1]. The treatment response to antidepressants takes various trajectories for each patient [2], and in most cases, prolonged treatment is required for depressive symptoms to achieve remission [3].

During the course of long-term treatment, there is a subgroup of individuals with depression who do not respond adequately to therapeutic interventions; they are referred to as difficult-to-treat depression (DTD). DTD is characterized by persistent depressive symptoms that continue to cause a significant burden despite usual treatment efforts [4]. DTD is suspected when at least two treatment failures occur, and this condition shares similarities with the concept of treatment-resistant depression (TRD) [4]. The DTD also applies the chronic illness model [5], which considers psychosocial functioning and quality of life from the patient's perspective during the persistence of depressive symptoms [4]. Therefore, DTD is a concept that encompasses TRD as well as persistent depressive disorder (PDD), in which depressive symptoms persist and become chronic.

* Corresponding author. Department of Neuropsychiatry, Kansai Medical University, Osaka, Japan.
E-mail address: katom@takii.kmu.ac.jp (M. Kato).

https://doi.org/10.1016/j.heliyon.2023.e20917
Received 15 November 2022; Received in revised form 7 October 2023; Accepted 11 October 2023
Available online 13 October 2023

Prolonged depressive symptoms have been reported to represent a higher burden on individual patients and the economy [6]. For example, patients with chronic depressive symptoms, such as those with persistent depressive disorder (PDD), have a significantly higher prevalence of current depressive symptoms, and a higher average number of episodes than patients with non-chronic MDD. Furthermore, it has been reported that patients with PDD have limited benefits from psychotherapy and pharmacotherapy, and are highly resistant to treatment. From an economic perspective, patients with PDD have a higher risk of having their activities limited by psychological problems, leading to decreased labor productivity, than non-chronic MDD. Moreover, patients with PDD have higher rates of outpatient mental health care utilization [6,7], and tend to spend more days in the hospital, increasing the cost of healthcare. Therefore, it is important to prevent the chronicity of depressive symptoms and relapse after remission, when treating patients with MDD. However, pharmacotherapy for PDD is associated with a higher incidence of adverse events compared to placebo and poses challenges in clinical management [8]. Non-pharmacological treatment, specifically psychotherapy, has demonstrated effectiveness in terms of efficacy and acceptability, particularly when used in conjunction with pharmacotherapy [9]. Moreover, the decision-making process regarding the choice between pharmacotherapy and psychotherapy relies on various factors, including patient age and baseline depression levels [9]. Consequently, characterizing patients to tailor treatment approaches becomes advantageous in clinical practice, ultimately enabling the provision of more effective interventions.

Moreover, the misdiagnosis of bipolar disorder as depression often leads to the problem of providing inappropriate treatment for bipolar patients. Patients with bipolar disorder are misdiagnosed as having MDD. Actually, approximately 20 % of patients diagnosed with MDD have their diagnosis changed to bipolar disorder during the course of treatment [10]. This is because bipolar disorder presents depressive symptoms approximately 70–90 % of the time during symptomatic periods, and only a few manic or hypomanic symptoms [11,12]. Furthermore, the use of antidepressant monotherapy for the first depressive episode of bipolar disorder significantly increases the risk of switching mania [13]. It has also been reported that bipolar depression generally responds poorly to traditional antidepressants, which may also induce a switch to mania and/or cause rapid cycling over the long term [14]. Thus, the patients with bipolar disorder who are misdiagnosed with MDD often receive inappropriate treatment which may lead to long-term treatment.

Thus, it is clinically useful to characterize depressed patients with worse long-term outcomes such as DTD (PDD and TRD), and bipolar disorder. Previous clinical trials have been short-term, or cross-sectional studies that compared patients already diagnosed with PDD or TRD with a control group [6,7,15–20]. However, short-term clinical trials may miss cases of treatment-resistant or persistent depressive disorder, or individuals who later receive a diagnosis of bipolar disorder. Moreover, cross-sectional designs do not sufficiently answer clinical questions, because causality cannot be examined [17], and diagnostic accuracy is also a concern [6] because of possible limitations, such as recall bias. On the other hands, few studies have explored the relationship between therapeutic outcomes and patient characteristics over a long-term follow-up period [10–12]. In addition, randomized controlled trial (RCT) designs have the advantage of reducing various biases, but are difficult to perform for long periods. In particular, RCTs examining psychotherapy interventions have observed patients over a period ranging from 6 to 46 months [21]. In contrast, the intervention period for pharmacotherapy is relatively shorter, typically lasting 2–16 weeks [22]. Therefore, a study that follows the long-term course of patients enrolled in an RCT may avoid the biases indicated above better than a naturalistic prospective trial. Although depression is a chronic illness with diverse outcomes over time, including sustained remission, treatment discontinuation due to side effects, and even a change in diagnosis to bipolar disorder, limited research has been conducted to track these trajectories. Within this context, we hypothesize that pretreatment clinical characteristics and the response to a six-week treatment period in previously untreated individuals with depression may serve as predictive factors for long-term outcomes. In this context, we conducted a two-year follow-up study of patients enrolled in a six-week RCT, to determine the clinical and sociodemographic characteristics associated with significant outcomes such as PDD, recovery, relapse, and bipolar disorder diagnosis in patients with MDD.

2. Methods

2.1. Patients and data collection

In this cohort study, we observed patients for two years who were enrolled in two different six-week RCT studies [23,24]. These two studies included 201 Japanese patients who had been diagnosed with MDD according to the DSM-IV criteria [25]. The first six weeks of the RCT were defined as the RCT phase, and the two years in which there were no restrictions on subsequent interventions were defined as the treatment as usual (TAU) phase. In the RCT phase, all patients were either drug-naive, or had a ten-day washout period before the random assignment. The patients were randomly assigned to either paroxetine or fluvoxamine in Study 1 [23], or paroxetine or milnacipran in Study 2 [24]. These antidepressants were increased to therapeutic doses between days 8 and 11 of the study. The therapeutic doses of the drugs were: fluvoxamine (150 mg/day), paroxetine (40 mg/day), and milnacipran (100 mg/day). There was no concomitant use of psychotropic medication, except for low-dose sleep-inducing hypnotics at bedtime. Depressive symptoms were evaluated at baseline and every two weeks until week six using the Hamilton Depression Scale (HAMD) [26]. Exclusion criteria were as follows: clinically significant unstable medical illness, pregnancy, principal psychiatric diagnosis other than major depression, and electroconvulsive therapy within the previous six months. The inclusion and exclusion criteria for both trials were identical.

In the TAU phase, patients were assessed for depressive symptoms at each visit using the Clinical Global Impressions Severity Scale (CGI-S) [27]. This is a three-item scale, with items assessing severity of illness, global improvement, and efficacy index, rated on a seven-point scale by the researcher. The CGI-S assesses the severity of a patient's illness in seven steps as follows: 1 = normal, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, and 7 = among the most extremely ill patients.

Treatment outcomes were categorized as treatment continuation with PDD (PDD) or without PDD (non-PDD), termination with recovery (recovery), relapse, bipolar disorder diagnosis, hospital transfer, or termination of an unknown reason. PDD was defined as a patient whose CGI-S score did not reach 1 in two years. Non-PDD was defined as a group that did not meet the study's definition of PDD, but remained in treatment for two years. Recovery was defined as termination of treatment due to symptom improvement. Relapse was defined as a worsening of the score to 2 or more points in patients who had maintained a CGI-S score of 1 for at least three months. Non-relapse was defined as a group that maintained a CGI-S score of 1 for at least three months, and the score did not worsen thereafter. Change in diagnosis to bipolar disorder was performed by the attending physician based on DSM-IV-TR criteria. Termination of an unknown reason was defined as the termination of self-discontinuation.

Clinical and social backgrounds, including sex, age, duration of illness, smoking, alcohol consumption, and family history of psychiatric conditions, were also assessed. This study was approved by the Institutional Review Board and Ethics Committee of Kansai Medical University (Kansai Medical University, No. 2017318, 05/Jun/2018). After a full description of the study, all participants provided written informed consent prior to entering the study.

2.2. Statistical analysis

The primary outcome of this study was to identify the factors related to PDD and recovery. The secondary outcome was to identify factors related to relapse, and changes in the diagnosis of bipolar disorder.

First, we performed univariate logistic regression analysis to identify the factors associated with outcomes after two years. Univariate logistic regression analysis was performed to eliminate the effects of confounding factors, and multiple logistic regression analysis was performed using factors that were significantly different. In this analysis, three outcomes–PDD group/recovery group, relapse, and bipolar disorder diagnosis–were used as dependent variables. Demographic data, such as sex, age, duration of illness, smoking, alcohol consumption, family history of a psychiatric condition, and each item of the HAMD at week six of the RCT phase as residual symptoms were analyzed as independent variables. The p-values were adjusted using the false discovery rate (FDR) to account for multiplicity.

Second, to use the factors extracted for clinical practice, receiver operating characteristic (ROC) curve analyses were performed to determine the area under the curve (AUC), and cut-off point of the three treatment outcomes. The Pearson's χ^2 test was performed to examine the rates of these outcomes and related factors.

Another secondary result was the percentage of severity of PDD and non-PDD over a two-year period, respectively. Therefore, we performed an independent sample *t*-test to determine the duration of each CGI-S score in the PDD and non-PDD groups.

Analyses were performed using SPSS software version 21.0 J (SPSS, Tokyo, Japan). All statistical tests were two-tailed, and statistical significance was set at $p < 0.05$.

3. Results

3.1. Description of the two-year outcomes

Out of the 201 patients initially enrolled in the RCT phase, a total of 197 patients were included in the study. This number excludes four patients whose medical records from the TAU phase could not be verified. Of these, 60 patients remained on treatment for two years, and 137 patients discontinued treatment. Among the 60 patients (30.5 %) who continued treatment for two years, 21 had PDD (10.7 %), and 39 had non-PDD (19.8 %). Twenty-three patients (11.7 %) experienced relapse, and three patients (1.5 %) had their diagnosis changed to bipolar disorder. Reasons for hospital discharge included recovery (n = 54, 27.4 %), transfer (n = 20, 10.2 %), and unknown reasons (n = 63, 32.0 %).

The duration of the current episode was 2.2 months longer in the PDD group than in the recovery group, and the HAMD total score at baseline was 3.3 points higher (Table 1). However, no statistical differences in the background or symptom characteristics at baseline were found between the relapse and non-relapse groups, or between the change and non-change in the bipolar disorder

Table 1
Demographic and clinical characteristics in PDD and recovery.

	PDD (n = 21)		Recovery (n = 54)		
	Mean	SD	Mean	SD	p
Age (years)	47.4	11.5	43.1	14.9	n.s.
Current episode (months)	4.76	3.85	2.54	2.4	<0.05
Age at first episode (years)	47.6	12.3	42.6	16.0	n.s.
HAMD 17 items total score at baseline of RCT phase	21.2	4.2	17.9	5.4	<0.05
	n	%	n	%	p
Sex (female)	10	47.6	20	37.0	n.s.
Smoking (yes)	8	38.1	20	37.0	n.s.
Drinking (yes)	7	33.3	16	29.6	n.s.
Family psychiatric history (yes)	2	9.5	1	1.9	n.s.

Note: PDD, persistent depressive disorder; HAMD, Hamilton Depression Scale; RCT, randomized controlled trial; SD, standard deviation; n.s., non-significance.

diagnosis groups.

Baseline and six-week depressive symptom severity during the RCT phase, as well as characteristic background factors, were compared between the completers (those who completed the study) and the discontinuations (those who discontinued the study). There were no significant differences in characteristic backgrounds between the two groups (Table 2). In the severity of depressive symptoms, discontinuations had significantly lower HAMD 17 items total scores at baseline and six weeks compared to completers (HAMD 17 items total score at baseline: Completers: 21.0 ± 4.8, Discontinuations: 18.5 ± 5.3, $p < 0.01$; HAMD 17 items total score at six weeks: Completers: 8.7 ± 6.5, Discontinuations: 5.9 ± 5.9, $p < 0.01$, respectively).

Incidentally, Study 1 had significantly younger age and age at first episode than Study 2 (age: study 1: 43.9 ± 14.9, study 2: 48.9 ± 14.9, $p < 0.05$; age at first episode: study 1: 40.0 ± 14.9, study 2: 48.9 ± 15.3, $p < 0.01$, respectively). Study 1 also had a significantly longer duration of the current episode (month) than Study 2 (Study 1: 4.1 ± 3.4, study 2: 2.5 ± 2.7, $p < 0.01$). However, there was no significant difference in the number of participants' previous episodes between Study 1 and Study 2 (study 1: 0.06 ± 0.30, study 2: 0.07 ± 0.26). Other background characteristics such as sex, smoking, drinking and family psychiatric history, and severity of depressive symptoms were not significant between the two studies.

3.2. Residual symptom-related factors associated with PDD and recovery

In a comparison of PDD and recovery, of the 75 PDD and recovery patients, univariate logistic regression analysis was performed on the 67 patients who were able to assess the HAMD score of six weeks at the RCT phase. Significant differences were found in the severity of 15 residual symptoms of HAMD: psychosis, suicide, early insomnia, sexual interest, psychomotor agitation, mid-term insomnia, insight, psychomotor retardation, depressed mood, anorexia, mental anxiety, physical anxiety, general physical symptoms, work and activity, and duration of illness six weeks after treatment. Factors used in the multiple logistic regression analysis were those with a p-value of 0.03 or less based on the FDR.

Multiple logistic regression analysis predicted a significant model for identifying PDD and recovery ($p < 0.01$, Nagelkerke's $R^2 = 0.70$, using a forward stepwise model). The following three factors were significantly correlated with PDD: insight (OR, 10.3; 95 % CI, 1.4–75.5), work and activities (OR, 7.8; 95 % CI, 1.8–33.8), and general somatic symptoms (OR, 7.1; 95 % CI, 1.5–32.8) (Table 3). Since the HAMD score for general somatic symptoms and insight had values of only 0 and 1 for all patients at six weeks of the RCT phase, the data were analyzed by treating 0 as no symptoms and 1 as the presence of symptoms, using a dummy variable approach.

Incidentally, univariate logistic regression analysis with relapse and change in diagnosis to bipolar disorder as dependent variables did not reveal any significant factors.

3.3. Cut-off point for the clinical use of extracted factors

ROC curve analysis showed that the AUC of the score of work and activities was 0.88 (95 % CI, 0.80–0.97, $p < 0.001$, Youden index = 0.61), and the cut-off value for the risk of PDD was 2 or more for HAMD work and activity scores (Fig. 1). For lack of general somatic symptoms, the AUC of the score was 0.86 (95 % CI, 0.75–0.86, $p < 0.001$, Youden index = 0.64), and the cut-off value for the risk of PDD was 1 or more for HAMD general somatic symptoms score. For lack of insight, the AUC of the score was 0.69 (95 % CI, 0.52–0.85, $p < 0.001$, Youden index = 0.37), and the cut-off value for the risk of PDD was 1 or more. for this score. For lack of insight and general physical symptoms, the maximum value of severity was 1, which could only be obtained as a binary value representing the presence or absence of symptoms, and the cut-off value for the risk of PDD was found to be when these symptoms were present. A chi-square test comparing the frequency of PDD using these cutoff values showed a significant interaction (insight: $X2\ (1) = 11.1$, $p < 0.01$, work and activities; $X2\ (1) = 24.6$, $p < 0.001$, general somatic symptoms; $X2\ (1) = 21.8$, $p < 0.001$, respectively) (Table 4).

We calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the presence or absence of lack of insight and general physical symptoms as well as work and activity thresholds derived from the ROC analysis as predictors of PDD over two years (Table 3). Among the 67 patients, 12 of the 17 subjects with two or more points in work and activities

Table 2
Demographic and clinical characteristics between completers and discontinuations.

	Completers (n = 61)		Dropouts (n = 136)		
	Mean	SD	Mean	SD	p
Age (years)	49.2	12.9	45.3	15.9	n.s.
Current episode (months)	3.9	3.7	3	2.9	n.s.
Age at first episode (years)	49.3	13.3	45	16.4	n.s.
HAMD 17 items total score at baseline of RCT phase	21	4.8	18.5	5.3	<0.01
HAMD 17 items total score at 6 weeks of RCT phase	8.7	6.5	5.9	5.9	<0.05
	n	%	n	%	P
Sex (female)	31	50.8	61	44.9	n.s.
Smoking (yes)	17	27.9	41	30.1	n.s.
Drinking (yes)	14	23	44	32.4	n.s.
Family psychiatric history (yes)	3	4.9	6	4.4	n.s.

Note: PDD, persistent depressive disorder; HAMD, Hamilton Depression Scale; RCT, randomized controlled trial; SD, standard deviation; n.s., non-significance.

Table 3
Extraction of related factors of persistent depressive disorder.

	β	OR	95 % CI		P
Score of Insight at six-weeks	2.34	10.3	1.42	75.5	<0.05
Score of work and activities at six-weeks	2.05	7.8	1.8	33.8	<0.01
Score of general somatic symptoms at six-weeks	1.96	7.1	1.5	32.8	<0.05

Note: $p < 2.0605 \times 10^{-9}$, Nagelkerke's $R^2 = 0.70$. using the forward stepwise model. CI, confidence interval.

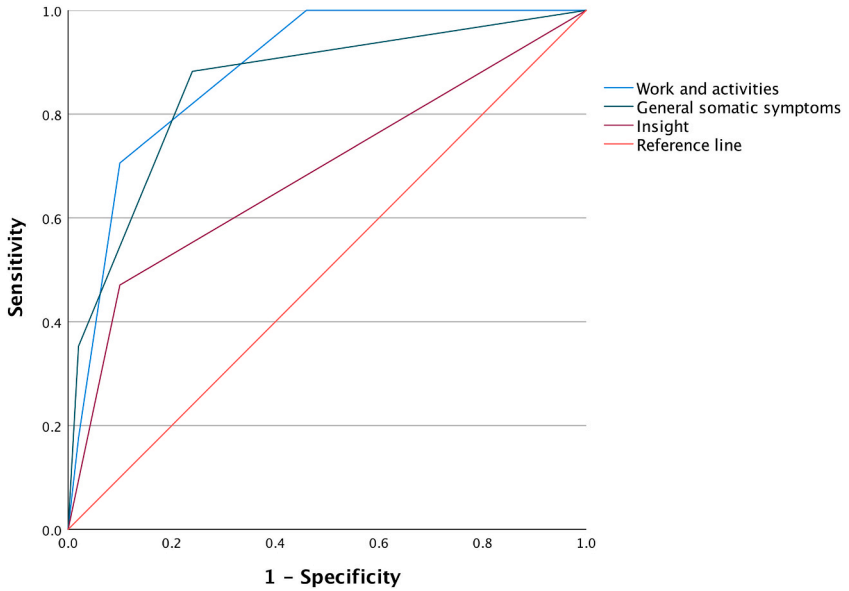


Fig. 1. ROC curve and AUC. ROC curve for work and activities, general somatic symptoms, and insight at six weeks in RCT phase based on the occurrence of PDD or Recovery at two years. N = 67. Cutoff score of work and activities = 2, AUC = 0.88, 95% confidence interval = 0.80–0.97, Youden index = 0.61, $p < 0.001$. Cutoff score of general somatic symptoms = 1, AUC = 0.86, 95% confidence interval = 0.75–0.96, Youden index = 0.64, $p < 0.001$. Cutoff score of insight = 1, AUC = 0.69, 95% confidence interval = 0.52–0.85, Youden index = 0.37, $p < 0.001$. Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve. PDD, persistent depressive disorder.

Table 4
Examination of cut-off points for PDD predictors.

n = 67		PDD	Recovery	Total	p						
Score of general somatic symptoms	yes	15	12	27	<0.001	χ^2	φ	Sensitivity	Specificity	PPV	NPV
	no	2	38	40		21.8	0.57	88.2	76	55.6	95
	Total	17	50	67							
n = 67		PDD	Recovery	Total	p						
Score of insight	yes	8	5	13	<0.01	χ^2	φ	Sensitivity	Specificity	PPV	NPV
	no	9	45	54		11.1	0.41	47.1	90	61.5	83.3
	Total	17	50	67							
n = 67		PDD	Recovery	Total	p						
Score of work and activities	2 points or more than	12	5	17	<0.001	χ^2	φ	Sensitivity	Specificity	PPV	NPV
	less than 1 point	5	45	50		24.6	0.61	70.6	90	70.6	90
	Total	17	50	67							

Note: PDD, persistent depressive disorder; PPV, Positive predictive value; NPV, Negative predictive value.

developed PDD, and of the 50 subjects with one or less in work and activities, 45 recovered (PPV, 70.6 %; NPV, 90.0 %; sensitivity, 70.6 %; specificity, 90.0 %). Fifteen of the 27 subjects with general somatic symptoms developed PDD, and of the 40 subjects with general somatic symptoms, 38 recovered (PPV, 55.6 %; NPV, 95.0 %; sensitivity, 88.2 %; specificity, 76.0 %). Eight of the 13 patients with symptoms of lack of insight developed PDD, and of the 54 patients with symptoms of lack of insight, 45 recovered (PPV, 61.5 %; NPV, 83.3 %; sensitivity, 47.1 %; specificity, 90.0 %).

3.4. Percentages of severity during the two years of the TAU phase

In Fig. 2, the percentages of severity during the two years of the TAU phase are shown in the seven CGI-S stage classifications for the 60 patients who were continuously attending the hospital. Three patients in the non-PDD group were excluded from the analysis due to a lack of available continuous data.

The percentage of the severity of depressive symptoms over a two-year period for all 57 patients was 0.8 % in the markedly or higher stage (CGI-S 5 to 7), 7.6 % in the moderate stage (CGI-S 4), 18.4 % in the mild stage (CGI-S 3), 32 % in the borderline stage (CGI-S 2), and 41.2 % in the asymptomatic stage (CGI-S 1).

The PDD group had significantly higher percentages of mild and moderate stages than the non-PDD group (CGI-S 3: PDD group: 38.3 ± 40.3, non-PDD group: 6.7 ± 13.6, $p < 0.01$; CGI-S 4: PDD group, 17.7 ± 31.0; non-PDD group, 1.7 ± 2.3; $p < 0.05$, respectively). However, the percentages in the markedly or higher stages were low in both the PDD group and non-PDD groups, and there was no significant difference in the percentages between the groups (CGI-S 5: PDD group, 0.8 ± 1.7; non-PDD group, 0.5 ± 1.3; CGI-S 6, PDD group; 0 ± 0, non-PDD group; 0.4 ± 1.2, CGI-S 7: PDD group; 0 ± 0, non-PDD group; 0 ± 0, non-significance). In addition, there was also no significant difference in the stage of borderline mental illness between the PDD and non-PDD groups (CGI-S 2: PDD group; 43.3 ± 41.7; non-PDD group; 25.5 ± 26.3, n.s.).

4. Discussion

Our study found that specific residual symptoms in the acute phase of treatment affected the long-term course of treatment for depression. It was suggested that the risk factors for PDD were loss of interest in work and activities, general somatic symptoms (fatigue), and lack of insight into the illness six weeks after the start of treatment. However, we could not identify any factors that contributed to relapse or change in the diagnosis of bipolar disorder using the residual symptoms after six weeks of treatment.

In previous studies, residual symptoms, especially fatigue and loss of interest, were strongly associated with the chronicity of depression [28,29]. PDD has also been reported to be associated with a higher proportion of periods of diminished motivation, anhedonia, and fatigue symptoms than non-PDD [30] and is strongly associated with impairments in social functioning [31]. Patients who suffer from low motivation and fatigue in the early stages of treatment may continue to have problems with these symptoms for the duration of the treatment. They may have continued to experience symptoms because their motivation and fatigue problems made it difficult for them to take actions to improve their depressive symptoms. Therefore, as Uher et al. (2014) reported, if this residual symptom is more than moderate, it is important to use non-pharmacological approaches such as behavioral activation therapy, to promote improvement in motivation [32].

It has also been reported that while patients with depression understand the need for treatment, they lack awareness of their depression and its causes of their symptoms [33]. In this study, the highest score at week six for lack of insight was 1 point (doubtful or trivial) and no patient had complete lack of insight. Therefore, it is possible that although the patients with PDD in this study understood the need for treatment and thus continued to be treated, their response to treatment was poor, owing to their lack of understanding of depression treatment. In this study, adherence was confirmed verbally at the time of consultation; however, blood levels were not measured. Therefore, inadequate disease awareness may lead to poor adherence.

To facilitate clinical use, we obtained cutoff points from the three risk factors for PDD. The cutoff point for general physical

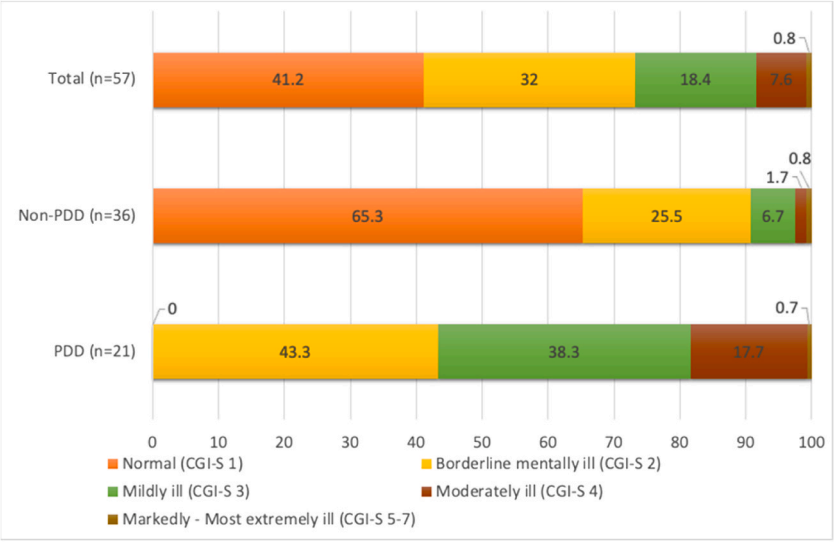


Fig. 2. The percentages of severity during the two years of the TAU phase. Note: TAU, treatment as usual; PDD, persistent depressive disorder; CGI-S, Clinical Global Impression Severity.

symptoms and lack of insight was the presence of symptoms, and that for work and activity was 2 points (moderate) or more. We expect that having a cutoff point for each factor for clinical use may help estimate the long-term course of treatment for depression.

Of the 67 patients with therapeutic outcomes of PDD or recovery, 74.6 % achieved recovery. If any of these three risk factors were below the threshold, it was highly predictive of the likelihood of achieving recovery within two years (NPV: 83.3–95.0 %). Among them, 25.3 % achieved PDD, and the PPV of PDD was between 55.6 % and 70.6 % when residual symptoms such as general physical symptoms (55.6 %) and lack of insight (61.5 %) remained or when work and activity (70.6 %) were more than moderate at six weeks after treatment. This suggests that assessing general physical symptoms, lack of insight, and work and activity six weeks into treatment may be useful in predicting outcomes over the next two years.

In this study, the reported prevalence of PDD was 10.7 %, which was lower than that reported in previous studies. Herrman et al. (2022) reported that the prevalence of PDD ranges from 12 % to 61 %, although the duration of observation and treatment settings vary [34]. This may be because our study was conducted on patients who participated in an RCT, and the setting was different from that of any previous study.

Furthermore, patients who continued to visit the hospital had depressive symptoms for approximately 58.8 % of the two-year period. A previous study reported that 59 % of the patients had depressive symptoms during the 12-year treatment period [35]. Although our study differed from theirs in terms of the shorter observation period, the proportion of the duration of illness was similar. In the PDD group, depressive symptoms were assessed as borderline (CGI-S 2) in 43.3 % of the periods, and mild (CGI-S 3) in 38.3 % of the periods. Furthermore, the period assessed as moderate or severe (CGI-S 4–7) accounted for 18.5 % of the time. This revealed that although PDD has chronic symptoms, more than 80 % of the total duration of symptoms is considered mild or less.

In the present study, we showed that the percentage of patients who had their diagnosis changed from depression to bipolar disorder was 1.5 %. To the best of our knowledge, this is the first report on the transition from diagnosis to bipolar disorder using Japanese data. This result is a lower rate of diagnostic change compared to previous studies [36]. Li et al. (2012) reported that 7.6–12.1 % of patients with MDD had their diagnosis changed to bipolar disorder an average of 1.89–2.98 years after being diagnosed with MDD [36]. The difference between our study and theirs may be due to the diagnostic accuracy. Li et al. (2012) conducted a longitudinal study of the rate at which patients diagnosed with MDD had their diagnosis changed to bipolar disorder using a national database [36], whereas in our study, the diagnosis was made by experienced psychiatrists based on structured interviews for enrollment in the RCT. This difference may have resulted in the lower rate of diagnostic change for bipolar disorder in this study. Furthermore, previous studies have shown that early age at illness onset is a robust predictor of mania or hypomania in MDD [10]. However, in the present study, the age at illness onset was 40 years and older than in previous studies. This difference may have also resulted in a lower diagnostic range for bipolar disorder in this study.

This study has several limitations. First, 32.0 % of the patients in this study terminated treatment for unknown reasons during the follow-up period. PDD may be present in patients who have discontinued treatment; however, the current analysis is limited because it does not include their data. Regarding the intensity of symptoms during acute treatment among individuals who completed and those who discontinued treatment, the increased symptom severity observed in the completers indicates that a higher symptom severity did not correlate with therapy termination. This implies that the group of discontinuers did not comprise a greater number of patients diagnosed with PDD.

Second, the frequency of visits and use of antidepressants varied among the patients, and treatment was not standardized. The lack of control over the frequency of visits and treatments is considered a limitation. However, because the subjects in this study participated in the RCT and were followed continuously, the accuracy of the diagnosis and severity assessment and the standardization of acute-phase drug therapy were more accurate than those of conventional retrospective studies.

Third, as mentioned above, this study verbally confirmed adherence at the time of the consultation. However, we did not rigorously assess adherence by measuring blood levels. Therefore, another limitation of this study is that inadequate antidepressant efficacy may have occurred due to hidden low adherence.

Fourth, there were some differences in the demographic and clinical characteristics of patients enrolled in the two RCTs used in this study. Although, the mean differences in the items that actually showed significant differences were small. Therefore, it is plausible that the observed differences may not carry clinical relevance.

In summary, the items extracted as characteristics of PDD included decreased motivation, fatigue, and lack of insight into illness as residual symptoms. We believe that attention should be paid to these residual symptoms, as well as ways to improve them within six weeks. Specifically, patients predisposed to PDD exhibit residual symptoms according to the subsequent HAMD six weeks post-initiation of acute phase treatment, with work and activities scores of at least 2, general somatic symptoms scores of no less than 1, or insight scores of a minimum of 1. Individuals without PDD encountered depressive symptoms of mild or greater intensity for approximately 10 % of the two-year duration. Conversely, individuals diagnosed with PDD demonstrated depressive symptoms exceeding mild intensity for over half of the same two-year timeframe. In addition, very few patients had their diagnosis changed from depression to bipolar disorder in this study. The stricter diagnosis based on structured interviews may have contributed to the lower rate of diagnostic change for bipolar disorder.

Funding statement

This work was supported by Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number JP18K13360, and JP22K13844 awarded to Yosuke Koshikawa.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Yosuke Koshikawa: Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Ai Onohara:** Writing – review & editing, Investigation, Data curation. **Masataka Wakeno:** Writing – review & editing, Resources. **Yoshiteru Takekita:** Writing – review & editing, Resources. **Toshihiko Kinoshita:** Writing – review & editing, Resources, Funding acquisition. **Masaki Kato:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We sincerely thank the patients and their families who participated in the study. We also thank Ms. Namiko Kiku and Ms. Noriko Shimasita for providing raw data input for computer analysis. We also thank Ms. Atsuko Yamamoto for her useful comments and suggestions regarding the manuscript. We would like to thank Editage (www.editage.com) for the English language editing.

References

[1] C.L. Vandeleur, S. Fassassi, E. Castelao, J. Glaus, M.F. Strippoli, A.M. Lasserre, D. Rudaz, S. Gebreab, G. Pistis, J.M. Aubry, J. Angst, M. Preisig, Prevalence and correlates of DSM-5 major depressive and related disorders in the community, Psychiatr. Res. 250 (2017) 50–58, https://doi.org/10.1016/j.psychres.2017.01.060.

[2] R. Gueorguieva, A.M. Chekroud, J.H. Krystal, Trajectories of relapse in randomised, placebo-controlled trials of treatment discontinuation in major depressive disorder: an individual patient-level data meta-analysis, Lancet Psychiatr. 4 (2017) 230–237, https://doi.org/10.1016/S2215-0366(17)30038-X.

[3] D.N. Klein, N.J. Santiago, Dysthymia and chronic depression: introduction, classification, risk factors, and course, J. Clin. Psychol. 59 (2003) 807–816, https://doi.org/10.1002/jclp.10174.

[4] R.H. McAllister-Williams, C. Arango, P. Blier, K. Demyttenaere, P. Falkai, P. Gorwood, M. Hopwood, A. Javed, S. Kasper, G.S. Malhi, J.C. Soares, E. Vieta, A. H. Young, A. Papadopoulos, A.J. Rush, The identification, assessment and management of difficult-to-treat depression: an international consensus statement, J. Affect. Disord. 267 (2020) 264–282, https://doi.org/10.1016/j.jad.2020.02.023.

[5] A.J. Rush, S.T. Aaronson, K. Demyttenaere, Difficult-to-treat depression: a clinical and research roadmap for when remission is elusive, Aust N Z J Psychiatry 53 (2019) 109–118, https://doi.org/10.1177/0004867418808585.

[6] J. Nubel, A. Guhn, S. Mullender, H.D. Le, C. Cohrdes, S. Kohler, Persistent depressive disorder across the adult lifespan: results from clinical and population-based surveys in Germany, BMC Psychiatr. 20 (2020) 58, https://doi.org/10.1186/s12888-020-2460-5.

[7] J.M. Rubio, J.C. Markowitz, A. Alegria, G. Perez-Fuentes, S.M. Liu, K.H. Lin, C. Blanco, Epidemiology of chronic and nonchronic major depressive disorder: results from the national epidemiologic survey on alcohol and related conditions, Depress. Anxiety 28 (2011) 622–631, https://doi.org/10.1002/da.20864.

[8] R. Meister, A. von Wolff, H. Mohr, M. Harter, Y. Nestoriuc, L. Holzel, L. Kriston, Comparative safety of pharmacologic treatments for persistent depressive disorder: a systematic review and network meta-analysis, PLoS One 11 (2016), e0153380, https://doi.org/10.1371/journal.pone.0153380.

[9] T.A. Furukawa, O. Efthimiou, E.S. Weitz, A. Cipriani, M.B. Keller, J.H. Kocsis, D.N. Klein, J. Michalak, G. Salanti, P. Cuijpers, E. Schramm, Cognitive-behavioral analysis system of psychotherapy, drug, or their combination for persistent depressive disorder: personalizing the treatment choice using individual participant data network metaregression, Psychother. Psychosom. 87 (2018) 140–153, https://doi.org/10.1159/000489227.

[10] J.G. Fiedorowicz, J. Endicott, A.C. Leon, D.A. Solomon, M.B. Keller, W.H. Coryell, Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder, Am J Psychiatry 168 (2011) 40–48, https://doi.org/10.1176/appi.ajp.2010.10030328.

[11] L.L. Judd, H.S. Akiskal, P.J. Schettler, J. Endicott, J. Maser, D.A. Solomon, A.C. Leon, J.A. Rice, M.B. Keller, The long-term natural history of the weekly symptomatic status of bipolar I disorder, Arch. Gen. Psychiatr. 59 (2002) 530–537, https://doi.org/10.1001/archpsyc.59.6.530.

[12] L.L. Judd, H.S. Akiskal, Pamela J. Schettler, W. Coryell, J. Endicott, Jack D. Maser, David A. Solomon, A.C. Leon, M.B. Keller, A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder, Arch Gen Psychiatry 60 (2003) 261–269, https://doi.org/10.1001/archpsyc.60.3.261.

[13] C.K. Chen, L.S. Wu, M.C. Huang, C.J. Kuo, A.T. Cheng, Antidepressant treatment and manic switch in bipolar I disorder: a clinical and molecular genetic study, J Pers Med 12 (2022), https://doi.org/10.3390/jpm12040615.

[14] G.S. Leverich, L.L. Altshuler, M.A. Frye, T. Suppes, S.L. McElroy, P.E. Keck Jr., R.W. Kupka, K.D. Denicoff, W.A. Nolen, H. Grunze, M.I. Martinez, R.M. Post, Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers, Am J Psychiatry 163 (2006) 232–239, https://doi.org/10.1176/appi.ajp.163.2.232.

[15] C. Blanco, M. Okuda, J.C. Markowitz, S.M. Liu, B.F. Grant, D.S. Hasin, The epidemiology of chronic major depressive disorder and dysthymic disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions, J. Clin. Psychiatry 71 (2010) 1645–1656, https://doi.org/10.4088/JCP.09m05663gry.

[16] F.H. Gronemann, M.B. Jorgensen, M. Nordentoft, P.K. Andersen, M. Osler, Socio-demographic and clinical risk factors of treatment-resistant depression: a Danish population-based cohort study, J. Affect. Disord. 261 (2020) 221–229, https://doi.org/10.1016/j.jad.2019.10.005.

[17] L. Holzel, M. Harter, C. Reese, L. Kriston, Risk factors for chronic depression–a systematic review, J. Affect. Disord. 129 (2011) 1–13, https://doi.org/10.1016/j.jad.2010.03.025.

[18] S. Ildirli, Y.B. Sair, F. Dereboy, Persistent depression as a novel diagnostic category: results from the menderes depression study, Noro Psikiyatr Ars 52 (2015) 359–366, https://doi.org/10.5152/npa.2015.7589.

[19] T. Mogi, A. Yoshino, The multiple diagnoses of comorbid anxiety disorders and higher interpersonal sensitivity predict treatment-resistant depression, Asian J Psychiatr 26 (2017) 131–135, https://doi.org/10.1016/j.ajp.2017.02.005.
[20] D. Souery, P. Oswald, I. Massat, U. Bailer, J. Bollen, K. Demyttenaere, S. Kasper, Y. Lecrubier, S. Montgomery, A. Serretti, J. Zohar, J. Mendlewicz, Group for the Study of Resistant, Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study, J. Clin. Psychiatry 68 (2007) 1062–1070, https://doi.org/10.4088/jcp.v68n0713.
[21] S. Ijaz, P. Davies, C.J. Williams, D. Kessler, G. Lewis, N. Wiles, Psychological therapies for treatment-resistant depression in adults, Cochrane Database Syst. Rev. 5 (2018) CD010558, https://doi.org/10.1002/14651858.CD010558.pub2.
[22] N.A. Nunez, B. Joseph, M. Pahwa, R. Kumar, M.G. Resendez, L.J. Prokop, M. Veldic, A. Seshadri, J.M. Biernacka, M.A. Frye, Z. Wang, B. Singh, Augmentation strategies for treatment resistant major depression: a systematic review and network meta-analysis, J. Affect. Disord. 302 (2022) 385–400, https://doi.org/10.1016/j.jad.2021.12.134.
[23] M. Kato, Y. Ikenaga, M. Wakeno, G. Okugawa, K. Nobuhara, T. Fukuda, K. Fukuda, J. Azuma, T. Kinoshita, Controlled clinical comparison of paroxetine and fluvoxamine considering the serotonin transporter promoter polymorphism, Int. Clin. Psychopharmacol. 20 (2005) 151–156, https://doi.org/10.1097/00004850-200505000-00005.
[24] M. Wakeno, M. Kato, G. Okugawa, T. Fukuda, Y. Hosoi, Y. Takekita, M. Yamashita, S. Nonen, J. Azuma, T. Kinoshita, The alpha 2A-adrenergic receptor gene polymorphism modifies antidepressant responses to milnacipran, J. Clin. Psychopharmacol. 28 (2008) 518–524, https://doi.org/10.1097/JCP.0b013e31818455fc.
[25] APA, Diagnostic and Statistical Manual of Mental Disorders, fourth ed., American Psychiatric Association, Washington, DC, 1994.
[26] M. Hamilton, Development of a rating scale for primary depressive illness, Br. J. Soc. Clin. Psychol. 6 (1967) 278–296.
[27] W. Guy, EC-DEU Assessment Manual for Psychopharmacology, Revised CGI Clinical Global Impressions, US Department of Health, 1976, pp. 76–339.
[28] M.S. Cepeda, J. Reps, P. Ryan, Finding factors that predict treatment-resistant depression: results of a cohort study, Depress. Anxiety 35 (2018) 668–673, https://doi.org/10.1002/da.22774.
[29] R. Uher, R.H. Perlis, N. Henigsberg, A. Zobel, M. Rietschel, O. Mors, J. Hauser, M.Z. Dernovsek, D. Souery, M. Bajs, W. Maier, K.J. Aitchison, A. Farmer, P. McGuffin, Depression symptom dimensions as predictors of antidepressant treatment outcome: replicable evidence for interest-activity symptoms, Psychol. Med. 42 (2012) 967–980, https://doi.org/10.1017/S0033291711001905.
[30] C.I. Hung, C.Y. Liu, C.H. Yang, Persistent depressive disorder has long-term negative impacts on depression, anxiety, and somatic symptoms at 10-year follow-up among patients with major depressive disorder, J. Affect. Disord. 243 (2019) 255–261, https://doi.org/10.1016/j.jad.2018.09.068.
[31] L. Culpepper, P.R. Muskin, S.M. Stahl, Major depressive disorder: understanding the significance of residual symptoms and balancing efficacy with tolerability, Am. J. Med. 128 (2015) S1–S15, https://doi.org/10.1016/j.amjmed.2015.07.001.
[32] R. Uher, J.L. Payne, B. Pavlova, R.H. Perlis, Major depressive disorder in DSM-5: implications for clinical practice and research of changes from DSM-IV, Depress. Anxiety 31 (2014) 459–471, https://doi.org/10.1002/da.22217.
[33] L.S. Woon, S.I. Khoo, A. Baharudin, M. Midin, Association between insight and internalized stigma and other clinical factors among patients with depression: a cross-sectional study, Indian J Psychiatry 62 (2020) 186–192, https://doi.org/10.4103/psychiatry.IndianJPsychiatry_612_19.
[34] H. Herrman, V. Patel, C. Kieling, M. Berk, C. Buchweitz, P. Cuijpers, T.A. Furukawa, R.C. Kessler, B.A. Kohrt, M. Maj, P. McGorry, C.F. Reynolds, M. M. Weissman, D. Chibanda, C. Dowrick, L.M. Howard, C.W. Hoven, M. Knapp, H.S. Mayberg, B.W.J.H. Penninx, S. Xiao, M. Trivedi, R. Uher, L. Vijayakumar, M. Wolpert, Time for united action on depression: a lancet–world psychiatric association commission, Lancet 399 (2022) 957–1022, https://doi.org/10.1016/s0140-6736(21)02141-3.
[35] L.L. Judd, H.S. Akiskal, J.D. Maser, P.J. Zeller, J. Endicott, W. Coryell, M.P. Paulus, J.L. Kunovac, A.C. Leon, T.I. Mueller, J.A. Rice, M.B. Keller, A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders, Arch Gen Psychiatry 55 (1998) 694–700, https://doi.org/10.1001/archpsyc.55.8.694.
[36] C.T. Li, Y.M. Bai, Y.L. Huang, Y.S. Chen, T.J. Chen, J.Y. Cheng, T.P. Su, Association between antidepressant resistance in unipolar depression and subsequent bipolar disorder: cohort study, Br. J. Psychiatry 200 (2012) 45–51, https://doi.org/10.1192/bjp.bp.110.086983.