Clinical Significance of the Number of Depressive Symptoms in Major Depressive Disorder: Results from the CRESCEND Study

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Our study aimed to establish the relationship between the number of depressive symptoms and the clinical characteristics of major depressive disorder (MDD). This would enable us to predict the clinical significance of the number of depressive symptoms in MDD patients. Using data from the Clinical Research Center for Depression (CRESCEND) study in Korea, 853 patients with DSM-IV MDD were recruited. The baseline and clinical characteristics of groups with different numbers of depressive symptoms were compared using the χ^2 test for discrete variables and covariance (ANCOVA) for continuous variables. In addition, the scores of these groups on the measurement tools were compared by ANCOVA after adjusting the potential effects of confounding variables. After adjusting the effects of monthly income and history of depression, a larger number of depressive symptoms indicated higher overall severity of depression (F [4, 756] = 21.458, $P < 0.001$) and higher levels of depressive symptoms (F [4, 767] = 19.145, $P < 0.001$), anxiety symptoms (F [4, 765] = 12.890, $P < 0.001$), and suicidal ideation (F [4, 653] = 6.970, $P < 0.001$). It also indicated lower levels of social function (F [4, 760] = 13.343, $P < 0.001$), and quality of life (F [4, 656] = 11.975, $P < 0.001$). However, there were no significant differences in alcohol consumption (F [4, 656] = 11.975, $P < 0.001$). The number of depressive symptoms can be used as an index of greater illness burden in clinical psychiatry.

Keywords: Number; Major Depressive Disorder (MDD); Depressive Symptoms; Anxiety Symptoms; Suicidal Ideation

INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent condition with staggering economic costs and a strong likelihood of recurrence and chronicity (1-4). In the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (5), MDD is defined by the presence of necessary features (depressive mood or marked diminished pleasure) and 5 or more symptoms among 9 characteristic features, namely depressive mood, anhedonia, change in appetite or weight, sleep problems, psychomotor problems, fatigue or loss of energy, excessive self-reproach or guilt, impaired decision-making and thoughts of death. In terms of fulfilling the diagnostic criteria for MDD in the DSM-IV and Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (5,6), 227 different combinations of 5 ≥ depressive symptoms are calculated (7). Because of this heterogeneity, the diagnosis of MDD has been seen as equivalent to a language game whose elements are connected not by an essential process but by family resemblance as viewed in Wittgensteinian philosophy (8). In relation to the complexity of the diagnostic criteria for MDD, it has been proposed that the requirement for either low mood or anhedonia might be omitted, since depressed patients with ≥ 5 depressive symptoms without low mood and anhedonia are rare (9). Nonetheless, all 9 symptoms in the diagnostic criteria of the DSM-IV were retained as independent domains in the DSM-5 (6).

The psychometric properties of the number of depressive symptoms have been analyzed in relation to the operational definition of MDD (9,10). A greater number of depressive symptoms were encountered in women with depression than in men with

depression (11). Use of the DSM framework pointed to a higher diagnostic threshold for MDD in Koreans than Americans, since low energy and difficulty in concentrating tended to preponderate over depressive mood and thoughts of death among Koreans with MDD (12). However, the clinical significance of the number of depressive symptoms as specified by the DSM-IV or DSM-5 diagnostic criteria for MDD has been little studied. Using data from the Clinical Research Center for Depression (CRESCEND) study in Korea (13,14), we have examined the clinical significance of the number of depressive symptoms in patients for operationally defining MDD.

Thus, the specific objectives of our study were (i) to examine the frequencies of different numbers of depressive symptoms in MDD patients and (ii) to determine how this number relates to the clinical characteristics of the patients.

MATERIALS AND METHODS

Subjects and procedure
As described elsewhere (13,14), from January 2006 to August 2008, 1,183 patients beginning psychiatric treatment for first-onset or recurrent depressive disorder were recruited from 18 general hospitals (16 university-affiliated general hospitals and 2 general hospitals) to the CRESCEND study, which was the first and largest clinical study of a nationwide sample of depressed patients in Korea. Our inclusion criteria were (i) age ≥ 18 years and ≤ 80 years, (ii) diagnosis of non-psychotic MDD according to the DSM-IV (5), confirmed by the Structural Clinical Interview based on DSM-IV Axis I Disorders (SCID-I) (15), and (iii) total score on the 17-item HAMD ≥ 8 points, consistent with the severity classification of Zimmerman et al. (16). Our exclusion criteria were (i) age < 18 years or > 80 years and (ii) diagnosis of MDD with psychotic features, dysthymic disorder, or depressive disorder not otherwise specified. Finally, 853 patients with non-psychotic MDD were enrolled in our study.

Baseline characteristics and assessment scales
Baseline data were collected for age (years), gender, marriage, educational attainment (years), occupation, monthly income, health care, religious affiliation, age-at-onset of first depressive episode (years), history of depression, medical comorbidity, family history of depression, previous history of suicidal attempts and outpatient enrollment. Using the SCID-I (15), the presence/absence of each of 9 depressive symptoms was evaluated based on the diagnostic criteria for MDD in the DSM-IV (4). The levels of depression, anxiety, suicidal ideation, global severity, social function, quality of life, and drinking were evaluated by the 17-item Hamilton Depression Rating Scale (HAMD) (17), Hamilton Anxiety Rating Scale (HAMA) (18), Scale for Suicidal Ideation (SSI-Beck) (19), Clinical Global Impression of Severity (CGI-S) (20), Social and Occupation Functional Assessment Scale (SO-

FAS) (21), WHO Quality of Life assessment instrument-abbreviated version (WHOQOL-BREF) (22), and Alcohol Use Disorder Identification Test (AUDIT) (23), respectively. All the scales had been formally translated into Korean, and their psychometric validity had been clearly confirmed in the Korean population (24-29). Higher scores on the HAMD, HAMA, BPRS, SSI-Beck, CGI-S, and AUDIT, and lower scores on the SOFAS and WHO-QOL-BREF indicate more severe symptoms or greater illness burden.

Statistical analysis
The χ^2 test was used to compare depressive symptom profiles between men and women. In addition, the study subjects were divided into 5 groups by the number of depressive symptoms: N = 5, 6, 7, 8, and 9, respectively. Using ANCOVA for continuous variables in the baseline characteristics and the χ^2 test for discrete variables in these characteristics, differences among the groups were analyzed. After adjustment of the effects of potential confounding variables, using the analysis of covariance (ANCOVA), differences in the scores on the measurement scales among the groups were analyzed. In addition, Fisher's least significant difference test for the ANCOVA was used to perform post-hoc analyses of the differences in the scores on measurement scales. Statistical significance was set at $P < 0.01$ (two-tailed) in all tests, to reduce the likelihood of familywise error due to multiple comparisons.

Ethics statement
The protocol and consent forms of the CRESCEND study were approved by the relevant institutional review board of The Catholic University of Korea, Catholic Medical Center (receipt number: CUMC07U001). Before the initiation of the CRESCEND study, written informed consent was obtained from all the subjects. All sociodemographic and clinical data were collected, and scores on the measurement scales were evaluated by certified research coordinators under the supervision of clinical psychiatrists in the research centers.

RESULTS

Frequencies of different numbers of depressive symptoms
Among the 853 MDD patients, there were 270 (31.7%), 239 (28.0%), 175 (20.5%), 107 (12.5%), and 62 (7.3%) with 5, 6, 7, 8, and 9 depressive symptoms, respectively. In addition, 838 (98.2%), 794 (93.1%), 294 (34.5%), 713 (83.6%), 604 (70.8%), 722 (84.6%), 568 (66.6%), 536 (62.8%), and 354 (41.5%) of the patients presented with depressive mood, anhedonia, change in appetite or weight, sleep problems, psychomotor problems, fatigue or loss of energy, excessive self-reproach or guilt, impaired decision-making and thoughts of death, respectively. As shown in Table 1, no significant differences were found between men and women for

Table 1. Gender differences in the DSM-IV depressive symptom profiles

Symptoms	No. (%) of subjects				
	Total (n = 853)	Men (n = 205)	Women (n = 648)	Statistical coefficients	P value
Depressive mood	835 (98.2)	197 (96.6)	638 (98.8)	$\chi^2 = 4.301$	0.038
Anhedonia	791 (93.1)	192 (94.1)	599 (92.7)	$\chi^2 = 0.466$	0.495
Change in appetite or weight	293 (34.5)	73 (35.8)	220 (34.1)	$\chi^2 = 0.205$	0.651
Sleep problems	710 (83.5)	168 (82.4)	542 (83.9)	$\chi^2 = 0.270$	0.603
Psychomotor problems	603 (70.9)	146 (71.6)	457 (70.7)	$\chi^2 = 0.051$	0.821
Fatigue or loss of energy	719 (84.6)	176 (86.3)	543 (84.1)	$\chi^2 = 0.585$	0.444
Excessive self-reproach or guilt	568 (66.8)	138 (67.6)	430 (66.6)	$\chi^2 = 0.082$	0.774
Impaired decision-making	534 (62.8)	133 (65.2)	401 (62.1)	$\chi^2 = 0.647$	0.421
Thoughts of death	353 (41.5)	90 (44.1)	263 (40.7)	$\chi^2 = 0.741$	0.389

Table 2. Comparison of the baseline characteristics of the groups by number of depressive symptoms

Parameters	Total samples (n = 853)	Number of depressive symptom profiles					Statistical coefficients	P value
		5 (n = 270)	6 (n = 239)	7 (n = 175)	8 (n = 107)	9 (n = 62)		
Age, mean (SD) yr	48.4 (15.0)	47.1 (14.9)	48.4 (14.7)	49.8 (15.5)	50.2 (15.7)	46.9 (13.0)	F = 1.480	0.206
Women, n (%)	646 (76.0)	206 (76.6)	183 (77.2)	135 (77.1)	78 (72.9)	44 (71.0)	$\chi^2 = 1.792$	0.774
Married, n (%)	533 (68.8)	173 (68.1)	152 (70.4)	108 (70.1)	65 (68.4)	35 (62.5)	$\chi^2 = 1.472$	0.832
Education, mean (SD) yr	10.4 (4.7)	10.8 (4.3)	10.3 (4.4)	10.3 (4.8)	9.9 (4.3)	10.5 (4.6)	F = 0.931	0.445
Employed, n (%)	586 (75.6)	197 (77.6)	170 (78.7)	115 (74.7)	67 (70.5)	37 (66.1)	$\chi^2 = 5.812$	0.214
Monthly income < 2,000 USD, n (%)	383 (49.0)	116 (30.3)	117 (30.5)	88 (54.7)	41 (40.6)	21 (37.5)	$\chi^2 = 9.805$	0.044
National health insurance, n (%)	775 (90.9)	249 (92.2)	219 (91.6)	161 (92.0)	94 (87.9)	52 (83.9)	$\chi^2 = 5.860$	0.210
Religious affiliation, n (%)	531 (62.5)	179 (66.3)	142 (59.7)	104 (60.1)	69 (64.5)	37 (59.7)	$\chi^2 = 3.286$	0.511
Age-at-onset*, mean (SD) yr	37.4 (16.0)	36.4 (15.6)	36.5 (15.3)	40.9 (16.3)	37.1 (18.0)	36.6 (15.5)	F = 1.094	0.359
History of depression, n (%)	373 (44.2)	115 (43.1)	95 (40.1)	72 (41.6)	52 (49.5)	39 (62.9)	$\chi^2 = 12.234$	0.016
Medical comorbidity, n (%)	269 (31.5)	82 (30.4)	85 (35.6)	50 (28.6)	35 (32.7)	16 (27.4)	$\chi^2 = 3.234$	0.519
Family history of depression, n (%)	117 (13.7)	33 (12.2)	31 (13.0)	24 (13.7)	19 (17.8)	10 (16.1)	$\chi^2 = 2.403$	0.662
Previous suicidal attempt, n (%)	189 (22.2)	52 (19.3)	54 (22.6)	37 (21.1)	26 (24.3)	20 (32.3)	$\chi^2 = 5.398$	0.249
Outpatient enrollment, n (%)	665 (78.0)	203 (75.2)	190 (79.5)	144 (82.3)	84 (78.5)	44 (71.0)	$\chi^2 = 5.227$	0.265

*n = 371. n, number of subjects.

Table 3. Comparison of the scores on the measurement scales in the groups by number of depressive symptoms

Measurement scales	Total samples (n = 853)	Number of depressive symptom profiles					Statistical coefficients*	Adjusted P value*	Post-hoc analyses[†]
		5 (n = 270)	6 (n = 239)	7 (n = 175)	8 (n = 107)	9 (n = 62)			
HAMD, mean (SD)	20.6 (5.7)	18.7 (5.4)	20.6 (5.7)	21.1 (4.9)	22.2 (5.6)	25.1 (6.6)	F = 19.145	< 0.001	a < b = c = d < e
HAMA, mean (SD)	19.8 (8.6)	17.6 (8.8)	19.0 (7.7)	21.0 (8.6)	22.3 (8.3)	25.6 (9.1)	F = 12.890	< 0.001	a = b < c = d < e
SSI-Beck, mean (SD)	11.0 (8.7)	9.6 (8.3)	11.0 (8.7)	10.5 (8.8)	13.6 (8.9)	16.5 (8.1)	F = 6.970	< 0.001	a = b = c < d = e
CGI-S, mean (SD)	4.7 (1.0)	4.4 (1.0)	4.7 (0.9)	5.0 (1.0)	5.0 (0.9)	5.4 (0.9)	F = 21.458	< 0.001	a < b = c = d < e
SOFAS, mean (SD)	56.6 (10.9)	59.8 (10.0)	56.1 (10.3)	55.9 (10.8)	54.1 (10.9)	50.0 (11.2)	F = 13.343	< 0.001	a > b = c = d > e
WHOQOL-BREF, mean (SD)	63.6 (10.3)	66.4 (10.3)	61.6 (9.3)	62.9 (9.3)	61.4 (9.3)	57.2 (9.6)	F = 11.975	< 0.001	a > b = c = d = e
AUDIT[‡], mean (SD)	10.5 (9.0)	10.5 (9.4)	11.5 (9.0)	9.8 (8.6)	8.9 (7.7)	10.9 (9.8)	F = 0.528	0.715	-

*Adjusted for the effects of monthly income and history of depression; [†]a, N = 5; b, N = 6; c, N = 7; d, N = 8; e, N = 9, N mean number of depressive symptom profiles; [‡]n = 305. N, number of depressive symptoms; n, number of subjects; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; SSI-Beck, Scale for Suicidal Ideation; CGI-S, Clinical Global Impression of severity; SOFAS, Social and Occupational Functional Assessment Scale; WHOQOL-BREF, WHO Quality of Life assessment instrument-abbreviated version; AUDIT, Alcohol Use Disorder Identification Test.

any of the DSM-IV depressive symptoms.

Baseline characteristics of the groups by number of depressive symptoms

As shown in Table 2, monthly income ($\chi^2 = 9.805$, $P = 0.044$) and history of depression ($\chi^2 = 12.234$, $P = 0.016$) tended to differ according to number of depressive symptoms, although the differences were not statistically significant. However, there were

no significant differences in the other baseline demographic or clinical variables between the 5 groups.

Scores on measurement scales by number of depressive symptoms

As shown in Table 3, after adjustment for the effects of monthly income and history of depression, greater numbers of depressive symptoms were associated with higher scores on the HAMD

(F [4, 767] = 19.145, $P < 0.001$), HAMA (F [4, 765] = 12.890, $P < 0.001$), SSI-Beck (F [4, 653] = 6.970, $P < 0.001$), and CGI-S (F [4, 756] = 21.458, $P < 0.001$), and lower scores on the SOFAS (F [4, 760] = 13.343, $P < 0.001$), and WHOQOL-BREF (F [4, 656] = 11.975, $P < 0.001$). However, there was no significant difference in scores on the AUDIT (F [4, 267] = 0.528, $P = 0.715$).

DISCUSSION

In summary, MDD patients with 5 symptoms were the most frequent in terms of number of depressive symptoms. After adjustment of the effects of monthly income and history of depression, a greater number of depressive symptoms were found to indicate higher levels of depressive symptoms, anxiety symptoms, suicidal ideation, and global severity, as well as poorer social function and quality of life.

No unique gender-specific patterns of depressive symptoms were identified in our study. Partly contradicting our findings, the Research on Asian Psychotropic Prescription Patterns for Antidepressants (REAP-AD) study of patients with depressive disorders in 10 Asian countries/regions showed that loss of interest and fatigue were more prevalent in men than women, and suicidal thoughts/acts were more prevalent in women than men (30). These differences between the two sets of findings may be associated with the high incidence of suicidal behavior in women in rural regions of mainland China (31). Thus, we may speculate that ethno-cultural influences can contribute to gender-specific patterns of depressive symptoms in patients with depressive disorders. Also, in a report on the age-related patterns of depressive symptoms, which was presented separately from the other findings of the CRESCEND study, the lower age-groups tended to have higher rates of current suicidal ideation. Hence, specific therapeutic approaches to the enhanced suicidal risk in younger persons may be needed in Korea. In conclusion, age- and gender-related patterns of depressive symptoms have not been clearly established in MDD patients in Korea. In addition, the clinical significance of number of depressive symptoms may be greater than that of the presence/absence of individual symptoms.

To our knowledge, the neurobiological underpinnings of the relationship between number of depressive symptoms and severity of depression have been little studied. However, an inverse relationship was found between left orbito-frontal cortex activity in magneto-encephalography and net number of DSM-IV diagnostic criteria for depressive personality disorder (unusual mood, poor self-concept, self-criticism, negativity towards others, pessimism, and feelings of guilt) in patients with borderline personality disorder. The association can be explained by dysfunctional modulation of emotional information in the orbito-frontal cortex and translation to the prefrontal cortex (32). Thus, these may be neural correlates of the positive relationship between the number of depressive symptoms and the severity of depressive disorders.

Greater number of depressive symptoms was associated with greater severity of anxiety symptoms and suicidal ideation. Higher gray matter volume in the right temporal cortex has been found in MDD patients with anxiety symptoms than in those without anxiety symptoms (33). Thus, the positive relationship between the number of depressive symptoms and severity of anxiety symptoms has been related to the neural correlates of anxiety symptoms. Also a significant relationship has been proposed between MDD and anxiety symptoms, based on prospective studies (34). Hence, comorbid cases in which MDD preceded anxiety symptoms can be explained by the shared etiology model, whereas comorbid cases in which anxiety symptoms preceded MDD can be explained by the direct causation model (35). Since we observed a relationship between number of depressive symptoms and severity of anxiety symptoms in a cross-sectional study, our ability to provide specific explanations of the relationship is limited. Moreover, a reduced gray matter density in the fronto-striato-limbic network has been shown in MDD patients with high risk of suicide relative to healthy controls (36). Hence, we may speculate that dysregulations of emotion and motivation contribute to the positive relationship between number of depressive symptoms and severity of suicidal ideation. A psychological autopsy study has reported that, among the DSM-IV depressive symptoms, not only suicidal ideation but also weight or appetite loss, insomnia, feelings of worthlessness, and inappropriate guilt are risk factors for suicide completions in the context of MDD (37). Since these depressive symptoms indicating suicidal completion, were not examined in our study, the clinical significance of the positive relationship between the number of depressive symptoms and severity of suicidal ideation is unclear. In addition, irritability/impulsivity may be a mediating factor between number of depressive symptoms and severity of anxiety symptom and suicidal ideation, since irritability has been associated with anxiety, and greater severity and impulsivity has been related to suicide outcome in MDD (38).

The lack of a significant relationship between number of depressive symptoms and scores on the AUDIT is partly consistent with the non-linear relationship between depression severity and alcohol consumption in previous studies (39). Greater number of depressive symptoms reflects more severe depression and lower social function and quality of life. A possible relationship has been reported between number of depressive symptoms and increased risk of academic problems in a large cohort of North Carolina college students (40).

Our study has several limitations. Firstly, psychiatric comorbidity has a potential effect on the relationship between the number of depressive symptoms and scores on the measurement tools. Secondly, no measurement tools covering the cognitive domains were employed. Thirdly, inter-rater reliability for as-

sessing depressive symptoms and using measurement tools was not assessed. Despite these limitations, our study has the virtue of pioneering investigation of the relationship between the number of depressive symptoms and the clinical characteristics of MDD.

In conclusion, a greater number of depressive symptoms indicates more serious depression and is associated with more severe anxiety symptoms and suicidal ideation. The relationship between number of depressive symptoms and the severity of anxiety symptoms and suicidal ideation may be mediated by irritability/impulsivity.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conception and design of the study: Park SC, Kim JM, Jun TY, Lee MS, Kim JB, Yim HW, Park YC. Analysis of the data: Park SC, Park YC. Writing the first draft of the manuscript: Park SC, Sakong JK, Koo BH, Park YC. Revision of manuscript: Park SC, Sakong JK, Koo BH, Park YC. Agreement and acceptance of final manuscript: all authors.

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