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Gender Differences in the Clinical Characteristics of Psychotic Depression: Results from the CRESCEND Study

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Objective: To test whether there are gender differences in the clinical characteristics of patients with psychotic depression (PD).
Methods: Using data from the Clinical Research Center for Depression (CRESCEND) study in South Korea, we tested for potential gender differences in clinical characteristics among 53 patients with PD. The Psychotic Depression Assessment Scale (PDAS) and other psychometric scales were used to evaluate various clinical features of the study subjects. Independent *t*-tests were performed for normally distributed variables, Mann-Whitney U-tests for non-normally distributed variables, and χ^2 tests for discrete variables. In addition, to exclude the effects of confounding variables, we carried out an analysis of covariance (ANCOVA) for the normally distributed variables and binary logistic regression analyses for discrete variables, after adjusting the effects of marital status.
Results: We identified more prevalent suicidal ideation (adjusted odds ratio [aOR]=10.316, p=0.036) and hallucinatory behavior (aOR=8.332, p=0.016), as well as more severe anxiety symptoms (degrees of freedom [df]=1, F=6.123, p=0.017), and poorer social and occupational functioning (df=1, F=6.265, p=0.016) in the male patients compared to the female patients.
Conclusion: Our findings suggest that in South Korean patients with PD, suicidal ideation, hallucinatory behavior, and anxiety is more pronounced among males than females. This should be taken into consideration in clinical practice.

KEY WORDS: Psychotic depression; Gender; Suicidal ideation; Hallucinatory behavior; Illness burden.

INTRODUCTION

Psychotic depression (PD) is characterized by depression accompanied by both positive and negative psychotic symptoms.[1-5] Because the severity-psychosis hypothesis proposed that the psychotic symptoms resulted from the severity of depression, the specifier of 'with psychotic features' was confined to severe major depression in the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV). However, several studies have now demonstrated that psychotic symptoms can also accompany milder depressive states. Therefore, the specifier of 'with psychotic features' can now accompany mild, moderate and severe major depression, as well as dysthymia, according to the recently published DSM-5.[6-9] In addition to psychotic symptoms, several clinical features including psychomotor disturbance (agitation or retardation), anxiety symptoms, suicidal behavior, deficits in executive function, psychiatric comorbidity, and conversion to manic episodes have been reported to be more prevalent or greater in PD than in non-PD.[1,10,11]

Gender has been regarded as a significant factor influencing depression rate, symptom profile, treatment response, and illness course in depression, especially in non-PD. Hence, some gender-specific symptom constellations of non-PD have been identified. For example, in non-PD, depressed men are less likely than depressed women to suffer from increased appetite, weight gain,

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anxiety, interpersonal sensitivity, and somatic complaints.[12-14] Although many disagree with the idea, the concept of male depression syndrome has been proposed in non-PD.[15] However, it appears that potential differences in the clinical features of men and women with PD have been studied to a much lesser extent.[16-19] Fennig *et al.*[16] showed that female patients with PD were characterized by more frequent fatigue, psychomotor agitation, and systematized and mood-incongruent delusions than males, whereas male PD patients were characterized by more frequent feelings of worthlessness than females. In their 6-year follow-up of community death registers in the Amsterdam Study of the Elderly (AMSTEL). Welham *et al.*[18] showed that male patients with affective psychoses had a younger modal age-at-first-registration than females. In addition, Deligiannidis *et al.*[19] reported that female gender was associated with more frequent comorbid anxiety disorders as well as more frequent hallucinations and delusions with disorganization. However, they found no significant gender difference in treatment response. Finally, findings by Schoevers *et al.*[17] suggested that the mortality risk in males with PD was greater than that of females.

The aim of the present study was to cast further light on potential gender differences in the clinical characteristics of patients with PD, based on an analysis of data from the South Korean Clinical Research Center for Depression (CRESCEND) study.[4,5,7]

METHODS

Study Overview

As described elsewhere,[4,5,7] the CRESCEND study was the first large, prospective, observational clinical study of a nationwide sample of patients with depressive disorder in South Korea. The study subjects were recruited from 1,183 patients with first-onset or recurrent depressive disorder (major depression, dysthymia, and other non-specified depressive disorder), who were beginning psychiatric treatment, from January 2006 to August 2008, and were enrolled at one or other of the 18 participating centers in the CRESCEND study (16 university-affiliated hospitals and two general hospitals across South Korea). The CRESCEND study was approved by the institutional review board of The Catholic Medical Center (receipt number: CUMC07U001). All the study subjects gave written informed consent. Certified research coordinators collected and evaluated the demographic and clinical data of the study subjects under the supervision of clinical psychiatrists at each of the research centers.[4,5,7]

Psychotic Depression

Following the proposals of Keller *et al.*,[10] Lichtenberg and Belmaker,[20] and Østergaard *et al.*,[1] we defined PD, regardless of severity, as depressive disorder accompanied by delusions and/or hallucinations. The inclusion criteria were as follows: (i) age $\geq$18 years; (ii) diagnosis of major depression, dysthymia, or other non-specified depressive disorder within DSM-IV[8] confirmed by a Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I);[21] (iii) recorded presence of definite delusions and/or hallucinations; and (iv) availability of the fully completed Hamilton Depression Rating Scale (HAMD)[22] and Brief Psychiatric Rating Scale (BPRS).[23]

The Psychotic Depression Assessment Scale (PDAS)

Since the HAMD mainly focuses on depressive symptoms rather than psychotic symptoms, it is primarily useful for evaluating the symptom severity of the depressive domain of PD.[22] Conversely, the BPRS predominantly concentrates on psychotic symptoms, and only one item covers depressive symptoms.[23] Therefore, the 11-item PDAS, which combines the 6-item melancholia subscale (HAMD-6) of the HAMD (depressive mood, guilt feelings, work and activities, psychomotor retardation, psychic anxiety, and general somatic symptoms items) and the 5-item BPRS-5 subscale (hallucinatory behavior, unusual thought content, suspiciousness, blunted affect, and emotional withdrawal items), has been developed to assess the overall severity of the entire PD syndrome. The clinical validity, responsiveness and unidimensionality of the PDAS have been demonstrated, and the total score is therefore a valid measure for the symptom severity of PD.[2,3,24] In addition, the PDAS has been validated for differential diagnosis of PD and non-PD.[4] With a cut-off value of one, the total score on the BPRS-5 subscale of the PDAS reliably differentiates PD from non-psychotic depressive disorder.[5] Moreover, the HAMD-6 subscale is regarded as a 'depression ruler' and valid scale for outcome measures in clinical trials of depression.[2,25] Most items of the HAMD are scored on a 0-4 point Likert scale, whereas all items of the BPRS are scored on a 1-7 point Likert scale. Therefore, when calculating the total score on the BPRS-5 and the PDAS in the present study, scores on the BPRS-5 items were converted from scores from 1-7 to scores from 0-4 using the following formula: (BPRS score $-$ 1)$\times$2/3 in the PDAS. Similarly, when calculating the total score on the HAMD-6 and the PDAS, scores on

the general somatic item (range 0-2) were multiplied by 2.[2,3] In the statistical analyses, each of the scores on the PDAS items were transformed to a dichotomous variable (score of 0=absence of symptom, score of 1-4=symptom present).

Other Psychometric Scales

Structured interviews including the HAMD,[22] BPRS,[23] Hamilton Anxiety Rating Scale (HAMA),[26] Clinical Global Impression of severity (CGI-s),[27] and Social and Occupational Functioning Assessment Scale (SOFAS)[28] were used to evaluate depressive symptoms, positive and negative symptoms, anxiety symptoms, global severity, and social function, respectively. With a formal consensus meeting to guarantee the accurate application of psychometric assessments, all the evaluators undertook a training program twice a year. In addition, self-questionnaires including the World Health Organization Quality of Life questionnaire-abbreviated version (WHOQOL-BREF)[29] and the Alcohol Use Disorder Identification Test (AUDIT)[30] were used to evaluate quality of life and alcohol use, respectively. All psychometric scales have been formally translated into Korean and validated as reliable assessment tools in the relevant Korean populations.[31-36] Higher scores on the HAMD,[22] BPRS,[23] HAMA,[26] CGI-s,[27] and AUDIT[30] represent greater severity for each of symptoms, whereas lower scores on the SOFAS[28] and WHOQOL-BREF[29] represent poorer social function and quality of life, respectively.

Statistical Analyses

The distributions of continuous variables were tested for normality by the Kolmogorov-Smirnov test. The significance of gender differences in demographic and clinical characteristics and assessment scale scores were evaluated using the independent *t*-test for normally distributed variables, the Mann-Whitney U-test for non-normally distributed variables and the χ^2 test for discrete variables. The effects of potential confounding variables on gender differences were adjusted by means of analysis of covariance (ANCOVA) for normally distributed variables, and binary logistic regression analysis for discrete variables. In the binary logistic regression analysis, the female group was defined as the reference category of the covariate. In our study we found that the proportion of unmarried individuals was significantly greater among males than among females (Table 1). Since it has been reported that marriage has a moderating effect on the prevalence and psychological consequences of depression.[37-40] To exclude such an effect, we treated marriage as a covariate in our ANCOVA and binary logistic regression analysis. Statistical significance was set at $p<0.05$. All statistical analyses were performed with PASW Statistics 18.0 for Windows (IBM Co., Armonk, NY, USA).

RESULTS

Comparison of Demographic and Clinical Characteristics

A total of 53 PD patients from CRESCEND met the inclusion criteria for this study. Table 1 shows a comparison of the clinical characteristics of male and female PD

Table 1. Gender differences in demographic and clinical characteristics of patients with psychotic depression

Characteristic	Total sample (n=53)	Men (n=17)	Women (n=36)	Statistical coefficients	Unadjusted *p* value	Adjusted *p* value*
Age (yr)	40.7±15.2	38.0±16.4	42.0±14.7	*U*=258.000	0.360	-
Unmarried	17 (33.3)	10 (58.8)	7 (20.6)	χ^2=7.456	0.006	-
Unemployed	37 (72.5)	13 (76.5)	24 (70.6)	χ^2=0.197	0.657	0.570
Education attainment (yr)	12.2±4.0	13.4±3.0	11.7±4.3	*U*=238.500	0.194	-
Religious affiliation	33 (62.3)	10 (58.8)	23 (63.9)	χ^2=0.126	0.723	0.984
Monthly income <USD 2,000	33 (62.3)	11 (64.7)	22 (61.1)	χ^2=0.604	0.801	0.518
DSM-IV diagnosis				χ^2=0.147	0.701	0.803
Major depressive disorder	49 (92.5)	16 (94.1)	33 (91.7)			
Depressive disorder not otherwise specified	4 (7.5)	1 (5.9)	3 (8.3)			
Age at onset (yr)†	28.6±14.1	27.7±14.1	29.1±14.4	*U*=169.000	0.471	-
Outpatient enrollment	35 (66.0)	9 (52.9)	26 (72.2)	χ^2=1.914	0.167	0.324
History of depressive episode	43 (79.2)	14 (82.4)	28 (77.8)	χ^2=0.147	0.701	0.981
Current suicidal ideation	35 (70.0)	15 (93.8)	20 (58.8)	χ^2=6.320	0.012	0.036
History of attempted suicide	25 (47.2)	10 (58.8)	15 (41.7)	χ^2=1.364	0.243	0.422
Comorbid physical disease(s)	19 (35.8)	7 (41.2)	12 (33.3)	χ^2=0.309	0.578	0.430

Values are presented as mean±standard deviation or number (%).
DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition.
*Adjusted for the effect of marital status; †n=42.

patients. Current suicidal ideation was significantly more likely to be reported in men than women (adjusted odds ratio [aOR]=10.316, degrees of freedom [df]=1, p=0.036). However, there were no significant gender differences in diagnosis (aOR=1.376, df=1, p=0.803), age at onset of first-onset depressive episode (U=238.500, p=0.194), outpatient enrollment (aOR=0.516, df=1, p=0.324), history of depressive episodes (aOR=1.020, df=1, p=0.981), history of attempted suicide (aOR=1.685, df=1, p=0.422) and comorbid physical disease (aOR=1.708, df=1, p=0.430).

Comparison of PDAS Items

Table 2 presented a comparison of absence/presence of the various PDAS items among male and female PD patients. Hallucinatory behavior was significantly more likely to be reported in men than women (aOR=8.322, df=1, p=0.016). However, there were no significant gender differences in presence/absence of depressive mood (aOR=20,823,301.982, df=1, p=0.998), guilt feelings (aOR=0.904, df=1, p=0.903), work and activities (aOR=5,082.147, df=1, p=0.998), psychomotor retardation (aOR=2.769, df=1, p=0.206), psychic anxiety (aOR=6.750, df=1, p=0.142), general somatic symptoms (aOR=0.658, df=1, p=0.608), unusual thought content (aOR=3.840, df=1, p=0.196), suspiciousness (aOR=2.500, df=1, p=0.187), blunted affect (aOR=0.759, df=1, p=0.714), and emotional withdrawal (aOR=1.175, df=1, p=0.816).

In addition, there were no significant gender differences in the summed scores on the PDAS (U=200.000, p=0.079), HAMD-6 subscale (U=257.500, p=0.352) and BPRS-5 subscale (U=200.500, p=0.173).

Comparison of Assessment Scale Scores

Table 2 also compared the assessment scale scores of male and female PD patients. Men had significantly higher scores than women on the HAMA (F=6.123, df=1, p=0.017) and lower score on the SOFAS (F=6.265, df=1, p=0.016). However, there were no gender differences in total scores on the HAMD (U=220.000, p=0.100), BPRS (F=0.295, df=1, p=0.589), CGI-s (U=296.000, p=0.838), WHOQOL-BREF (F=1.167, df=1, p=0.287), and AUDIT (F=0.482, df=1, p=0.495).

DISCUSSION

In summary, this study of PD patients from the CRESCEND study showed that, after adjusting for the effects of marital status, male PD patients were more likely to display suicidal ideation and hallucinatory behavior,

Table 2. Gender differences in assessment scale scores of patients with psychotic depression

	Total sample (n=53)	Men (n=17)	Women (n=36)	Statistical coefficients	Unadjusted p value	Adjusted p value*
PDAS	14.0±4.7	15.6±5.7	13.1±4.0	U=200.000	0.079	-
HAMD-6	11.3±3.2	12.0±3.4	11.0±3.2	U=257.500	0.352	-
BPRS-5	2.6±2.6	3.6±3.3	2.1±2.1	U=200.500	0.173	-
Depressive mood	52 (98.1)	17 (100.0)	35 (97.2)	χ^2=0.481	0.488	0.998
Guilt feelings	40 (75.5)	14 (82.4)	24 (72.2)	χ^2=0.640	0.424	0.903
Work and activities	51 (96.2)	17 (100.0)	34 (94.4)	χ^2=0.981	0.322	0.998
Psychomotor retardation	39 (73.6)	14 (82.4)	25 (69.4)	χ^2=0.990	0.320	0.206
Psychic anxiety	49 (92.5)	16 (94.1)	33 (91.7)	χ^2=0.099	0.753	0.142
General somatic symptoms	43 (81.1)	13 (76.5)	30 (83.3)	χ^2=0.355	0.551	0.608
Hallucinatory behavior	11 (21.2)	6 (37.5)	5 (13.9)	χ^2=3.702	0.054	0.016
Unusual thought content	5 (9.6)	3 (18.8)	2 (5.6)	χ^2=2.219	0.136	0.196
Suspiciousness	18 (34.6)	7 (43.8)	11 (30.6)	χ^2=0.852	0.356	0.187
Blunted affect	17 (32.7)	6 (37.5)	11 (30.6)	χ^2=0.243	0.622	0.714
Emotional withdrawal	33 (63.5)	11 (68.8)	22 (61.1)	χ^2=0.279	0.598	0.816
HAMD	22.1±5.5	24.0±5.2	21.2±5.6	U=220.000	0.100	-
HAMA	22.6±9.5	26.7±10.4	20.6±8.6	t=2.229	0.030	0.017
BPRS	35.7±13.3	38.1±14.7	34.7±12.7	t=0.862	0.393	0.589
CGI-s	5.1±0.8	5.1±0.9	5.1±0.8	U=296.000	0.838	-
SOFAS	54.2±12.4	47.0±14.7	57.4±9.9	t=−2.583	0.017	0.016
WHOQOL-BREF	58.7±9.5	56.5±9.7	59.8±9.5	t=−1.050	0.300	0.287
AUDIT (n=26)	5.1±0.8	17.1±10.7	11.0±8.5	t=1.614	0.120	0.495

Values are presented as mean±standard deviation or number (%).
*Adjusted for the effect of marital status.
PDAS, Psychotic Depression Assessment Scale; HAMD-6, Hamilton 6-Item Melancholia Subscale; BPRS-5, Brief Psychiatric Rating Scale (BPRS)-5 Subscale of the Psychotic Depression Assessment Scale; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; CGI-s, Clinical Global Impression of severity; SOFAS, Social and Occupational Functional Assessment Scale; WHOQOL-BREF, World Health Organization Quality of Life assessment instrument-abbreviated version; AUDIT, Alcohol Use Disorder Identification Test.

had greater severity of anxiety symptoms, and poorer social and occupational functioning than female PD patiens.

Our finding of a higher prevalence of current suicidal ideation in men than women is consistent with the results of prior studies.[16,41-43] In addition, it could be part of the explanation as to why mortality rates in PD appears to be greater in men than in women.[16] However, we found no significant gender difference regarding the history of attempted suicide.

Of the 11 items of the PDAS, only hallucinatory behavior differed according to gender, with a higher prevalence among male patients. Conversely, in the study of pharmacotherapy of psychotic depression (STOP-PD), Deligiannidis *et al.*[19] found that the prevalence of hallucinations and delusions with disorganization were higher in women than in men. Although female gender was significantly associated with divorced or widowed marital status in the study of them, the authors did not the effects of marital status on clinical presentations. Hence, the difference between the results of this study and that of Deligiannidis *et al.*[19] may be due to a potential confounding effect of marital status.

The greater severity of overall anxiety symptoms in men than in women detected in our study also appears to be inconsistent with Deligiannidis *et al.*'s finding[19] of more common comorbid anxiety disorders in women compared to men. As mentioned above, this discrepancy could be caused by a confounding effect of marital status. Furthermore, in their reanalysis of data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) cohort, Cassano *et al.*[44] found a significant association between hallucinations and anxiety disorders, including posttraumatic stress disorder and panic disorder. Thus, in the light of the results from Deligiannids *et al.*[19] (hallucinations and anxiety more prevalent among women), Cassano *et al.*[44] (significant association between hallucinations and anxiety disorders in PD), and the results of the present study (higher prevalence of hallucinatory behaviour and higher severity of anxiety in men), we speculate that there may be a relationship between hallucinations and anxiety in PD, irrespective of gender.

The poorer social and occupational functioning in men compared to females detected in our study could be an epiphenomenon of the more severe psychopathology profile of the male patients (hallucinations, suicidal ideation and anxiety). Zaninotto *et al.*[45] reported that psychosis during the course of depression was significantly associated with poorer functioning in the areas of visual and verbal learning and execution. Thus, it may be that poorer cognitive functioning represents the explanatory link between the more severe psychopathology profile and the poorer social functioning in men with PD in the present study.

Our study has several limitations. Firstly, since our sample was small, the power to detect gender differences was limited. Secondly, because we did not adjust for multiple comparisons, the possibility of type II errors was increased. Thirdly, the study design was cross-sectional rather than longitudinal. Finally, since the rates of comorbid personality disorders and other mental disorders were not evaluated in the CRESCEND study, their potential effects on gender differences in clinical characteristics could not be taken into account. Despite these limitations, our study has the virtue of exploring gender differences in the clinical characteristics of patients with PD, a poorly investigated area. Our findings suggest that in South Korean patients with PD, suicidal ideation, hallucinatory behavior, and anxiety is more pronounced among males than females. This should be taken into consideration in clinical practice.

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