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The relationship between somatic symptoms and depression

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Abstract

OBJECTIVE: We investigated the influence of somatic symptoms on the severity and clinical outcomes in female Korean patients with major depressive disorder (MDD) in routine practice.

METHODS: Two hundred and seven female patients with MDD were prospectively recruited. Patients with somatic symptoms (PSS) was defined as a total score ≥ 10 on the Patient Health Questionnaire-15 (PHQ-15), others were classified as non PSS (NPSS). The PHQ-9 for de-pression, the Generalized Anxiety Disorder Scale (GAD-7) for anxiety, the Clinical Global Impression-Severity (CGI-S) for clinical status, and the Visual Analogue Scale (VAS) for health status were utilised.

RESULTS: Of 207 participants, 126 (60.9%) were PSS and 81 (39.1%) were classified as NPSS. The proportion of patients showing severe symptoms (65.1% vs. 24.7%) and recurrence of depression (74.6% vs. 49.4%), the CGI-S (4.6 vs. 4.1), the PHQ-9 (16.8 vs. 11.1), and the GAD-7 (8.3 vs 6.7) scores were significantly higher in PSS than in NPSS, while the VAS (39.4 vs. 51.2) was significantly lower in PSS than in NPSS. The improvement of depressive symptoms (−1.3 vs. −2.0) measured by the changes in CGI-S was also significantly less in PSS than in NPSS after 6 months treatment.

CONCLUSION: Our findings have shown the significant impact of somatic symptoms on the symptomatology as well as treatment outcomes in Korean female patients with MDD, indicating that clinicians should carefully evaluate somatic symptoms in patients with MDD in routine clinical practice. Due to the methodological shortcomings of the present study, further adequately powered and well-designed investigations are necessary.

ORIGINAL ARTICLE

INTRODUCTION

Major depressive disorder (MDD) is a prevalent mental illness including both emotional and somatic symptoms. Somatic symptoms are the leading cause of outpatient medical visits and the predominant reason why patients with MDD initially present in primary care (Kroenke 2003). According to previous studies, depression may be increased with the number of somatic symptoms in the adult population (Greden 2003; Kroenke *et al.* 1994); the number of physical symptoms and the presence/severity of depression were highly correlated. Furthermore, residual somatic symptoms were found to increase the risk of relapse of depression following treatments for depression (Greden 2003).

Evaluation of somatic symptoms in MDD patients has important implications in the treatment as well as diagnosis. Somatic symptoms accompanying MDD may interfere with the prognosis of MDD resulting in more severe depression, decline in quality of life (QoL), impairment of productivity, and increase in use of health resources (Demyttenaere *et al.* 2006; Bao *et al.* 2003). In addition, the onset of clinical response to antidepressants was significantly associated with the number of somatic symptoms at baseline, a greater number of which was a strong predictor of delayed antidepressant effects (Papakostas *et al.* 2004). In other studies, the presence of somatic symptoms contributed significantly to the occurrence of a new depressive episode several years later. In a long-term prospective population-based study (follow-up of approximately 13 years), the likelihood of developing new MDD onset was remarkably higher in patients who reported a history of somatic symptoms at baseline as well as during the follow-up period than those who never reported such somatic symptoms; a similar trend was also observed in responders and remitters (Addington *et al.* 2001).

However, few studies have investigated the influence of somatic symptoms on MDD in Asian compared with Western populations. Some studies have proposed that Asian patients tend to complain more about somatic symptoms and report less emotional symptoms than Western patients. In those studies, the tendency to show more comorbid somatic symptoms may be potentially involved in the lower rate of the overall MDD prevalence in Asian countries than in the Western world (Kalibatseva *et al.* 2014; Kalibatseva & Leong 2011; Ryder *et al.* 2008). In a large observational study with 909 MDD patients in six Asian countries, approximately 52% of patients were classified as having somatic symptoms, were more likely to be female, had relatively more medical comorbidities and more significantly severe MDD, as well as lower QoL than those without somatic symptoms (Lee *et al.* 2009). In addition, the response and remission rates increased proportionally with the severity of somatic symptoms, indicating that somatic symptoms may have prognostic value for treatment outcomes in MDD patients and should be considered when treating patients with MDD in clinical practice (Novick *et al.* 2013).

However, similar studies in the Korean population are lacking. Therefore, in this study we investigated the influence of somatic symptoms on MDD in Korean patients in terms of the relationship between the presence of somatic symptoms and the severity of MDD as well as the clinical outcomes after 6 months of treatment in a naturalistic setting.

METHODS

Patients

Subjects were enrolled at the outpatient clinic of Psychiatry, Bucheon St. Mary's Hospital, Korea. The MDD diagnosis was based on the criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). Diagnoses were made by highly experienced and board-certified psychiatrists. Patients who had a current medicosurgical condition and substance-related disorders – such as alcohol abuse and dependence – were excluded. The presence of comorbid illnesses was assessed by subjects' medications or history of diseases diagnosed by physicians. The present study followed the Declaration of Helsinki and ethical principles regarding human experimentation, and the study protocol was approved by the Institutional Review Board of Bucheon St. Mary's Hospital in Bucheon, Kyeonggi-Do, Korea (IRB approval number: HC10EESE0075).

Study design

The present investigation was a 6-month observational study in which various self- and clinician-rated scales were used. Sociodemographic parameters such as age, educational level, occupational status, duration of current episode, number of previous, living conditions and marital status were collected at baseline by person-to-person interviews based on the case report form from the study protocol.

This study utilised the Korean versions of the Patient Health Questionnaire-9 (PHQ-9) for the severity of MDD (Han *et al.* 2008; Kroenke *et al.* 2001), the PHQ-15 for the severity of somatisation (Han *et al.* 2009; Kroenke *et al.* 2002), and Generalized Anxiety Disorder Scale (GAD-7) (Kroenke *et al.* 2007) for anxiety. PHQ-9 scores of 5, 10, 15 and 20 represent cut-off points for mild, moderate, moderately severe, and severe depression, respectively. PHQ-9 validation has been established against an independent structured mental health professional interview. The PHQ-9 total score ≥ 10 had a sensitivity of 88% and a specificity of 88% for diagnosis of MDD (Han *et al.* 2008; Kroenke *et al.* 2001).

PHQ-15 scores of 5, 10 and 15 represent cut-off points for low, medium, and high somatic symptom severity, respectively. The PHQ-15 is a self-administered diagnostic instrument developed for detection of somatoform disorders that consists of 15 somatic symp-

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toms accounting for more than 90% of physical complaints (excluding upper respiratory tract symptoms). Higher scores on the PHQ-15 were found to be strongly associated with functional impairment, disability and healthcare utilisation (Han *et al.* 2009; Kroenke *et al.* 2002). A high internal reliability and construct validity strongly associated with functional status, disability days, and symptom-related difficulty have been elucidated. The criteria for the presence of somatic symptoms in the present study (total score ≥ 10 on PHQ-15) were defined as previously suggested (Han *et al.* 2009; Kroenke *et al.* 2002).

The GAD scores of 5, 10, and 15 are taken as the cut off points for mild, moderate, and severe anxiety, respectively. When used as a screening tool, further evaluation is recommended when the score is 10 or greater. Using the threshold score of 10, the GAD-7 has a sensitivity of 89% and a specificity of 82% for GAD. It is also moderately good at screening three other common anxiety disorders – panic disorder (sensitivity 74%, specificity 81%), social anxiety disorder (sensitivity 72%, specificity 80%), and post-traumatic stress disorder (sensitivity 66%, specificity 81%).

The visual analogue scale (VAS) was used for the assessment of health status (0–100). A VAS is a line, usually measuring 10 cm, with descriptors at each end (e.g. good to bad, none to severe). VAS has been widely used for the assessment of overall health status (Gudex *et al.* 1996) and QoL (Priestman & Baum 1976).

The changes in symptoms of MDD were assessed using Clinical Global Impression-Severity (CGI-S) score from baseline (day 0) to the end of treatment (6 months).

Subjects can be received one of following antidepressants as treatment an initiation for their current MDD episode based on their individual clinical situation (major antidepressants: escitalopram 10–20 mg/d, fluoxetine 20–40 mg/d, paroxetine controlled release (CR) 12.5–62.5 mg/d (paroxetine 10–40 mg/d), sertraline 100–150 mg/d, bupropion XL 150 mg/d or more, mirtazapine 15–45 mg/d, tianeptine 12.5–50 mg/d, venlafaxine XR 75–225 mg/d, or duloxetine 30 mg/d). Dose titration of antidepressants was fully dependent on clinical response and tolerability during the study as routine clinical practice. Antidepressant combination, augmentation agents such as psycho-stimulant or atypical antipsychotics, and other concomitant medications were not restricted as it was a naturalistic observational investigation. The ultimate type of therapy (eg, antidepressant monotherapy, combination therapy or augmentation therapy) was collected at the end of treatment.

Statistical analyses

For descriptive statistics, continuous variables were presented as mean values with standard deviations (SD) and categorical variables as frequencies. To examine group differences at baseline characteristics, statistical comparisons using analysis of variance (ANOVA) for continuous variables and Chi-square/Fisher's exact tests for categorical variables were performed.

Subjects were classified as patients with (PSS) and without (NPSS) somatic symptoms. The presence of somatic symptoms was based on the PHQ-15 total score (≥10 for PSS and <10 for NPSS). ANOVA was applied for comparisons of clinical symptom scores and other clinical parameters reported as continuous variables between NPSS and PSS at baseline. Chi-square/Fisher's exact tests were used for comparisons of the proportion of severity of depression and recurrence nature between NPSS and PSS.

To evaluate the influence of the somatic symptoms on the improvement of depression between PSS and NPSS (completer analysis only due to one post-baseline assessment with CGI-S), ANCOVA was performed using covariates of number of previous episode, and baseline scores of PHQ-9, CGI-S, and GAD-7. The improvement of MDD symptoms was measured using the CGI-S score from baseline (day 0) to the end of treatment (6 months). The influence of somatic symptoms on the severity and recurrence of MDD was described using odds ratios (ORs) with 95% confidence intervals (CIs). Pearson's correlation was used to evaluate the association between somatic and depressive symptoms assessed using the PHQ-15 and PHQ-9, respectively.

With these statistical parameters and after adjusting for covariates, the power of the sample to detect a large effect size (0.8) was 0.86, which corresponded to a difference of 0.7 in the mean difference in changes of CGI-S total scores from baseline to the end of treatment between PSS and NPSS. All statistical analyses were conducted using the NCSS 2007® and PASS 2008® software (Kaysville, UT, USA).

RESULTS

Demographic characteristics

Two hundred and seven patients were included in the present study. The average age was 42 years and approximately 52% were married; the others were widowed, unmarried, or separated. Approximately 59% of the patients had a higher than high school educational level. As for living status, 43% of patients were in upper and middle class. Approximately 36% of patients had a job.

Approximately 35% of the patients experienced their first MDD episode, while the others (65%) had recurrent episode. The mean scores on health status, anxiety, and depression measured by VAS, PHQ-9, PHQ-15, GAD-7, and CGI-S at baseline were 44.6, 14.6, 11.9, 7.6, and 4.4, respectively.

Relationship between somatic symptoms and MDD

Among the participants (n=207), 126 (60.9%) were classified as PSS and 95 (39.1%) as NPSS. No significant differences in age, duration of current episode,

Tab. 1. Clinical variables by the presence of the somatic symptoms based on the PHQ-15 total score between NPSS and PSS.

	Whole patients	Group	Values	F / *p* values
Age (years)	42.1 (15.9)	NPSS	41.1 (15.3)	0.434 / 0.511
		PSS	42.7 (16.4)	
NPE	1.4 (1.4)	NPSS	1.1 (1.2)	9.767 / 0.002
		PSS	1.7 (1.5)	
DCE	15.8 (16.9)	NPSS	14.7 (15.1)	0.549 / 0.460
		PSS	16.5 (17.9)	
CGI-S total	4.4 (1.2)	NPSS	4.1 (1.0)	5.893 / 0.016
		PSS	4.6 (1.3)	
PHQ-9 total	14.6 (6.3)	NPSS	11.1 (5.4)	52.315 / <0.0001
		PSS	16.8 (5.8)	
GAD-7	7.6 (3.4)	NPSS	6.7 (2.9)	11.897 / 0.001
		PSS	8.3 (3.5)	
Health status†	44.6 (18.3)	NPSS	49.2 (18.1)	6.825 / 0.01
		PSS	42.0 (18.1)	
Type of therapy‡			NPSS	PSS
Monotherapy	47 (39.8)		24 (53.3)	23 (31.5)
Combination/Augmentation	71 (60.2)		21 (46.7)	50 (68.5)

Data represent number (SD) or number (percent); Definition of presence of somatic symptoms (PHQ-15 total score ≥ 10); †measured by visual analog scale; PHQ, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder Scale-7; CGI-S, Clinical Global Impression-Severity; NPSS, patients without somatic symptoms, n=81; PSS, patients with somatic symptoms, n=126; NPE, number of previous episode; DCE, duration of current episode (weeks); ‡Fisher's exact-test, p=0.021, odds ratio (OR) for receiving combination/augmentation therapy in PSS=2.484, 95% confidence intervals (CIs), 1.079 to 5.757, reported at the end of treatment.

Tab. 2. Proportion of patients by depression severity and recurrence status between the NPSS and PSS at baseline.

	Whole patients	NPSS (N=81)	PSS (N=126)
Severity of depression†			
Minimal to mild	16 (7.7)	13 (16.0)	3 (2.4)
Moderate	89 (43.0)	48 (59.3)	41 (32.5)
Moderately severe and severe	102 (49.3)	20 (24.7)	82 (65.1)
Recurrence‡			
First onset	73 (35.3)	41 (50.6)	32 (25.4)
Recurrent	134 (64.7)	40 (49.4)	94 (74.6)

Data represent number (percent); Definition of presence of somatic symptoms (PHQ-15 total score ≥ 10); the PHQ-9 scores of 5, 10, and 15 were used for cut-off points for mild, moderate, moderately severe and severe depression, respectively; †Chi-square test, χ^2=36.426, df=2, p<0.0001, odds ratio (OR) for moderately severe and severe depression in PSS=5.684, 95% confidence intervals (CIs), 2.917 to 11.163; ‡Fisher's exact-test, p<0.0001, OR for recurrence in PSS=3.011, 95% CIs, 1.598 to 5.693; NPSS, patients without somatic symptoms; PSS, patients with somatic symptoms.

marital status, living status and educational level were observed between the PSS and NPSS (Table 1; marital status, occupational status, living status and education level data are not shown but available on request).

The proportion of patients showing severe depression symptoms (65.1% *vs*. 24.7%, p<0.0001) and recurrent nature of MDD (74.6% *vs*. 49.4%, p<0.0001), the CGI-S total score (4.6 *vs*. 4.1, p=0.016), the PHQ-9 total score (16.8 *vs*. 11.1, p<0.0001), and the GAD-7 score (8.3 *vs* 6.7, p=0.001) were significantly higher in PSS than in NPSS, while the health status measured by VAS (49.2 *vs*. 42.0, p=0.01) was significantly lower in PSS than in NPSS (Tables 1 and 2). The OR for moderately severe and severe depression in PSS was 5.684 (95% CI, 2.917–11.163) and the OR for recurrence in PSS was 3.011 (95% CI, 1.598–5.693) (Table 2). The total scores of PHQ-9 and PHQ-15 showed a significant positive correlation (r^2 = 0.535) based on Pearson's correlation coefficient (p<0.001).

Of 207 patients, 118 (57%; NPSS n=45 and PSS n=73) were followed up until the end of treatment (6 months). The likelihood of receiving polypharmacy such combination or augmentation therapy was significantly greater in PSS than in NPSS (68.5% vs 46.7%, p=0.021) during the study (Table 1). In the follow-up patients, the improvement of depressive symptoms measured by the changes in CGI-S total score from baseline to the end of treatment was significantly less in PSS than in NPSS (−1.3±1.2 *vs*. −2.0±1.3, F=5.707, p=0.019). A 48.8% and 28.3% reduction in CGI-S score from baseline to the end of treatment were observed in

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NPSS and PSS, respectively. The tendency of significant favouring NPSS over PSS in terms of improving depressive symptoms was also replicated when using the PHQ-15 total score of 5 for the presence of somatic symptoms as the cut-off point.

DISCUSSION

Somatic symptoms are highly prevalent in patients with MDD. The present study demonstrated somatic symptoms might significantly influence the severity, subjective health status, and treatment outcome of MDD. Notably, even mild somatic symptoms appeared to be significantly associated with worse outcomes of depression treatment. The results of the present study should enhance substantially the current understanding of the diagnostic and therapeutic approach to depression accompanied by somatic symptoms.

Our findings showing the influence of somatic symptoms on the severity, subjective health status, and treatment outcome of depression are consistent with previous reports that somatic symptoms were significantly related to severity, QoL, and treatment response in patients with depression (Vaccarino *et al.* 2008). Proper recognition of somatic symptoms is important for the diagnosis and management of depression as such symptoms are commonly involved in the clinical manifestation and may influence the treatment response. For example, in a large multinational study, approximately 70% of primary care patients with depression reported somatic symptoms as their primary reason for visiting a health professional (Simon *et al.* 1999), indicating that the presence of somatic symptoms may interfere negatively with proper and accurate diagnosis of depression. Furthermore, somatic symptoms were strongly associated with the development of residual depression symptoms, resulting in increased risk for subsequent early relapse and functional impairment (Paykel *et al.* 1995).

In accordance with the previous findings, the mean PHQ-15 total score of our subjects was approximately 12 and more than 60% of the patients were considered as having somatic symptoms, indicating an at least moderate severity of somatic symptoms along with depressive symptoms (PHQ-9=14.6), although the present study did not intend to target those patients. Therefore, our results showed that somatic symptoms are common in patients with depression in routine practice. The presence of somatic symptoms was significantly correlated with the severity of depression and the tendency of recurrence in the present study. In addition, our results showed that the presence of somatic symptoms was negatively correlated with the subjective health status, which is highly associated with patients' QoL; somatisation is related indirectly to significantly lower satisfaction in QoL (Kroenke 2003; Kroenke *et al.* 1994; Han & Pae 2014; Koh *et al.* 2014; Pae 2014).

Several studies reported that improvement of the somatic symptoms was significantly correlated with overall improvement of depressive symptoms, along with response and remission rates. This suggests a reciprocal interaction between somatic symptoms and core depressive symptoms; therefore, clinicians should identify, track, and target the somatic symptoms of patients with depression in routine clinical practice (McIntyre *et al.* 2006). Likewise, the present study demonstrated that somatic symptoms had a significant impact on the clinical outcomes of depression after 6 months of treatment; the improvement in depressive symptoms was almost twice as high in NPSS compared with PSS. These findings suggest that somatic symptoms may influence longer-term treatment outcomes, indicating a need for careful evaluation of somatic symptoms in patients with depression even when entering the continuation and maintenance treatment phase in clinical practice. Another notable finding was that even mild somatic symptoms had a significantly negative effect on the outcomes of depression treatment, indicating a need that clinicians should not neglect any complaints of somatic symptoms in patients with depression for better clinical outcomes. Interestingly, the probability of receiving polypharmacy such combination or augmentation therapy was approximately 1.5 times higher in PSS than in NPSS, indicating that clinicians may tactically, more aggressively approach when patients are comorbid with somatic symptoms in clinical practice.

Recent clinical evidence suggests that contemporary antidepressants such as selective serotonin reuptake inhibitors (SSRIs) may exert less profound effects on somatic compared to emotional symptoms (Nierenberg *et al.* 1999; Mallinckrodt *et al.* 2007). A greater number of somatic symptoms at baseline predicted a longer time to onset of a clinical response to the SSRI (eg, fluoxetine), regardless of the baseline severity of depression (Papakostas *et al.* 2004). Accordingly, the existence of somatic symptoms is particularly important as it may in part explain the adverse impact of somatic symptoms on the likelihood of patients with MDD achieving full remission (Papakostas *et al.* 2004; McIntyre *et al.* 2006). In addition, according to the results from a recent pooled analysis of two identical, independent, double-blind, placebo-controlled trials of duloxetine in patients with depression (Fava *et al.* 2004), the improvement of somatic symptoms of depression was associated with higher remission rates even after accounting for the improvement in core emotional symptoms. Potentially important differences in symptom response patterns were found between serotonin-norepinephrine reuptake inhibitors (SNRIs), such as duloxetine, and SSRIs—duloxetine demonstrated significantly greater (twofold) treatment effects than the SSRIs on improvement of somatic symptoms (Mallinckrodt *et al.* 2007). In this context, serotonin (5-HT) and norepinephrine (NE) are well-known to be involved in the control of various somatic symptoms (such as pain) *via* complex modulation of diverse neurotransmitter receptors involving development of

somatic symptoms such as pain. These results in modulation of neurotransmitter release, which enhances the efficacy of dual reuptake inhibitors (such as SNRIs) for treatment of physical symptoms than SSRIs, although the mechanisms of action are not clearly elucidated yet (Pae *et al.* 2009b; Marks *et al.* 2009; Marks *et al.* 2008; Pae *et al.* 2008; Luyten 2008; Pae *et al.* 2009a). In addition, a greater number of somatic symptoms was associated with an increased risk of developing further treatment resistance (Papakostas *et al.* 2003).

Our study had several strengths in comparison with previous works. For instance, some studies did not control for potential confounding clinical factors such as comorbid medical illnesses and gender effects (Papakostas *et al.* 2004). A majority of the previous studies investigated the association between somatic symptoms and depression, but did not utilise well-validated rating scales for the assessment of somatic symptoms, instead using specific somatic symptoms such as pain (Corruble & Guelfi 2000). In addition, the measurement of somatic symptom severity associated with depression symptomatology was often ignored, possibly resulting in faulty interpretation of results that could lead to meaningful clinical information being overlooked (Simon *et al.* 1999). Additionally, the follow-up duration was substantially longer in our study than in previous works, which is very important clinical issue since most patients with depression would need a long-term treatment due to its chronic and recurrent nature.

The present study had inevitable methodological limitations. The power of our sample appeared to be sufficient to detect a 0.7 magnitude of mean difference in changes of CGI-S total score from baseline to the end of treatment between PSS and NPSS. However, a larger sample size would provide better and valuable post hoc analysis findings to address meaningful clinical issues such as differential treatment outcomes by antidepressant type, onset age, and subtype of depression. The inherent weakness of PHQ-15 should also be considered as it does not cover all somatic symptoms in patients with depression, and the timeframe is confined to 'past month' (thus recall bias may exist when the visit interval is long, such as in the present study). Another limitation should be that, it is difficult to draw causal relationship between somatic symptoms and depression in the cross-sectional small study. For instance, severely depressed patients could present more severe symptoms across all dimensions of depressive symptoms including somatic symptoms. Finally, there were no sufficient F/up visits between baseline and the end of treatment since our study was naturalistic observational approach, which cannot provide with any details of clinical course.

CONCLUSION

Our results support the critical role of somatic symptoms in the severity of depression and treatment response in patients with depression. Hence, clinicians should pay careful attention to early detection and management of somatic symptoms in patients with depression in routine clinical practice, which will facilitate tailoring of individual therapies and making early decisions regarding further treatment options in difficult-to-treat patients.

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