A Comparison of Core Depressive Symptom Improvement with Anxiety Symptom Reduction for Depressed Patients Treated with Fluoxetine

Anxiety and depression are the most common coexisting psychological problems for patients with major depressive disorder (MDD). Treatment with antidepressant drugs can improve the symptoms of both anxiety and depression [1, 2]. Therefore, first-line psychopharmacological therapies may not be much different for an MDD patient with anxiety symptoms than for an MDD patient who has anxiety disorders with the full criteria of anxiety symptoms [3]. A meta-analysis of cognitive-behavioral therapy for youth depression was found effect sizes in anxiety symptom reduction (d = 0.39) that are less than those for depressive symptom improvement (d = 0.57) [4]. We explored the relationships between core depression symptoms and anxiety symptoms at each visit for inpatients receiving acute treatment with fluoxetine and attempted to know if depression and anxiety showed differential rates of changes. (Fluoxetine is a serotonin reuptake inhibitor as defined in the neuroscience-based nomenclature system [www.NbN.ECNP.org or www.NbN2r.com]). As the MDD patients received cognitive-behavioral therapy [4], we hypothesized that core depression symptoms would improve more quickly than anxiety symptoms during the acute treatment with fluoxetine.

As previously described in details [5], inpatients with *DMS-IV* MDD receiving fluoxetine for acute treatment entered the analysis. The current study was done from May 1, 2007, to February 28, 2010. Participants were considered eligible if they were patients newly hospitalized for acute treatment, were aged between 18 and 70 years, were physically healthy, had a baseline 17-item Hamilton Depression Rating Scale (HAMD-17) [6] score ≥18, and were not been diagnosed as treatment-resistant depression.

After a washout period of at least 72 hours, patients received open-label fluoxetine treatment at a fixed dose of 20 mg daily for 6 weeks. Symptom severity was assessed at baseline and at weeks 1, 2, 3, 4, and 6 using the HAMD-17. The HAMD-17 anxiety/somatization subscale [7], including six items namely the items for psychic anxiety (Item 10), somatic anxiety (Item 11), gastrointestinal somatic symptoms (Item 12), general somatic symptoms (Item 13), hypochondriasis (Item 15), and insight (Item 17), was used to measure the severity of anxiety symptoms. The HAMD-17 core factor subscale [8], including five items from the HAMD-17 namely the items for depressed mood (Item 1), feelings of guilt (Item 2), suicide (Item 3), work and activities-loss of interest or pleasures (Item 7), and psychomotor retardation (Item 8), was used to reflect the severity of depression symptoms.

Core factor subscale and anxiety/somatization subscale have different metrics. Effect size (d) is appropriate for comparisons involving scales with different metrics and is defined as the mean of difference between baseline and posttreatment scores for each measure, divided by the standard deviation (SD) of difference [9]. A d-value of 0.20 indicates a small effect size, 0.50 a medium effect size, and 0.80 a large effect size [10]. Pearson's correlation coefficient (r) was used to quantify the association between core factor subscale and anxiety/somatization subscale. A strong association is defined as a correlation greater than 0.70, moderate-to-substantial as a correlation of 0.30–0.70, and weak as a correlation less than 0.30 [11].

To compare the degrees of changes between core depression symptoms and anxiety symptoms after treatment, both the core factor subscale and anxiety/somatization subscale scores were converted to T-score units (mean ± SD = 50 ± 10). The T-score was calculated by the following formula [12]: $X_T = ([X_{raw} - \bar{X}_{pretreatment}]/SD_{pretreatment}) \times 10 + 50$. The generalized estimating equations (GEEs) method was applied to compare degrees of core depression symptom relief to those of anxiety symptom improvement at each assessment.

A total of 131 acutely ill inpatients with MDD were enrolled. Of the 131 participants, 126 (96.2%) had at least one postbaseline assessment at week 1 and entered the analyses. Twenty-seven (22.5%) were male, and 93 (77.5%) were female. The mean ± SD age was 45.1 ± 10.9 years. Table 1 contains raw scales, effect sizes, and T-scales of the core factor subscale and anxiety/somatization subscale at each visit. Acute treatment with fluoxetine resulted in large (d > 0.8) levels of changes in core factor subscale and anxiety/somatization subscale scores at weeks 1, 2, 3, 4, and 6. Core factor subscale was moderately correlated with core factor subscale (r ranging from 0.33 to 0.69) at each assessment.

Reduction of core factor subscale T-scores was significantly greater than that of anxiety/somatization subscale T-scores, which began at week 1 (estimate = −4.5, $p < 0.001$), and persisted through week 2 (estimate = −6.4, $p < 0.001$), 3 (estimate = −7.3, $p < 0.001$), 4 (estimate = −8.3, $p < 0.001$), and 6 (estimate = −8.7, $p < 0.001$). If GEE method was used to compare the degrees of core depression symptom relief to those of anxiety symptom improvement at weeks 1 2, 3, 4, and 6 for subjects (n = 112) who completed the 6-week trial, reduction of core factor subscale T-scores was still significantly greater than that of anxiety/somatization subscale T-scores at weeks 1 (estimate = −4.6, $p < 0.001$), 2 (estimate = −6.6, $p < 0.001$),

Table 1. Raw scores, effect sizes[a], and T-scores of 17-item Hamilton Depression Rating Scale, core factor subscale[b], and anxiety/somatization subscale[c] at each visit

	Week 0 (n = 126)	Week 1 (n = 126)	Week 2 (n = 120)	Week 3 (n = 117)	Week 4 (n = 116)	Week 6 (n = 112)
HAMD-17, mean ± SD	31.3 ± 6.5	21.4 ± 8.2	17.8 ± 8.1	16.4 ± 8.7	15.2 ± 8.4	13.6 ± 8.2
Effect size[a]		1.34	1.84	2.03	2.14	2.39
Core factor subscale[b], mean ± SD	12.2 ± 2.7	8.5 ± 3.5	6.9 ± 3.6	6.3 ± 3.9	5.7 ± 3.8	5.2 ± 3.7
Effect size[a]		1.28	1.80	1.73	1.76	1.90
Anxiety/somatization subscale[c], mean ± SD	9.8 ± 2.9	7 ± 2.9	6 ± 3	5.7 ± 3.1	5.3 ± 2.8	4.8 ± 2.6
Effect size[a]		1.14	1.33	1.48	1.58	1.66
r[d]	0.33**	0.54**	0.56**	0.62**	0.65**	0.69**
HAMD-17 T-score, mean ± SD	50.0 ± 10.0	34.7 ± 12.5	29.3 ± 12.5	27.2 ± 13.3	25.3 ± 12.9	22.9 ± 12.6
Core factor subscale T-score, mean ± SD	50.0 ± 10.0	36.5 ± 13.1	30.8 ± 13.2	28.4 ± 14.3	26.4 ± 14	24.5 ± 13.7
Anxiety/somatization subscale T-score, mean ± SD	50.0 ± 10.0	40.5 ± 9.9	36.9 ± 10.3	35.9 ± 10.6	34.5 ± 9.6	33.1 ± 9.0

**$p < 0.01$ significantly different using t-test
[a]Effect size = The difference in the mean score between baseline and each visit divided by the pooled standard deviation
[b]Core factor subscale = HAMD-17 Items 1, 2, 3, and 8
[c]Anxiety/somatization subscale = HAMD-17 Items 10, 11, 12, 13, 15, and 17
[d]r = Pearson correlation coefficient between core factor subscale and anxiety/somatization subscale
HAMD-17, 17-item Hamilton Depression Rating Scale; SD, standard deviation

3 (estimate = −7.3, $p < 0.001$), 4 (estimate = −8.1, $p < 0.001$), and 6 (estimate = −8.5, $p < 0.001$).

The first finding was that patients receiving fluoxetine had continual improvement over baseline in both core depression symptoms and anxiety symptoms (Table 1). Each effect size was large than 0.8. These results indicated that fluoxetine was effective both in treating core depression symptoms and in treating anxiety symptoms. The second was that core factor subscale was significantly ($p < 0.01$) correlated with core factor subscale at each assessment. It indicated that reciprocal associations existed between anxiety symptoms and core depression symptoms over time. This confirms previous reports that MDD patients with high levels of anxiety are associated with more severe depression [13, 14]. But the correlations were moderate (0.33–0.69). The third was that anxiety symptoms improvement was lagged behind rather than paralleled core depression symptoms improvement. Anxiety should therefore be regarded as a distinctive feature in MDD patients [15]. Fluoxetine can have a direct impact on anxiety symptoms.

Major limitation of this study includes short duration, single-arm, open-label study designed and only fluoxetine was used in the study. In further studies, whether other symptom domains have different time improvement from core depressive symptoms needs to be evaluated. (The study was approved by the institutional review board of the Kaohsiung Municipal Kai-Syuan Psychiatric Hospital [IRB protocol number = KSPH-2007-16 and date of approval = January 18, 2007] with the stipulation of obtaining the informed consent from the study participants.)

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Conflicts of Interest

The authors declare no conflicts of interest.

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