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Influence of painful physical symptoms in the treatment of Japanese patients with melancholic major depressive disorder: A prospective cohort study

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ABSTRACT

The aim of this study was to clarify how painful physical symptoms affect treatment outcomes in patients with melancholic major depressive disorder. The subjects comprised 100 consecutive Japanese outpatients with melancholic major depressive disorder who visited our clinic from October 2011 to October 2014. All subjects were interviewed for Diagnostic and Statistical Manual of Mental Disorders Axis 2, 3, and 4 and family history of major depressive disorder, and then grouped according to the presence of painful physical symptoms. We evaluated painful physical symptoms at baseline and after 12, 24, and 36 weeks of treatment and scores on the 17-item Hamilton Rating Scale for Depression, compared major depressive disorder remission between groups, and assessed responsiveness to antidepressants. The group with painful physical symptoms had a significantly more positive family history of major depressive disorder. The major depressive disorder remission rate was high in both groups, and no significant differences were observed. However, a significant relationship between major depressive disorder and painful physical symptoms remission was observed in the group with painful physical symptoms. A significantly higher number of remitted patients with painful physical symptoms (N=61) were administered serotonin–noradrenaline reuptake inhibitors, with significantly more receiving duloxetine than milnacipran.

1. Introduction

The presence of painful physical symptoms (PPS) associated with major depressive disorder (MDD) has recently received increased attention in the literature (Gerrits et al., 2015; Kishi et al., 2015; Bair et al., 2003). PPS in MDD are reported (Bair et al., 2003; Lee et al., 2009; Novick et al., 2013a, 2013b, 2015) to be very prevalent (50–76%), and are accompanied by more severe depressive symptoms and a poorer quality of life (Novick et al., 2013b, 2015). Most importantly, PPS in MDD are associated with a poorer treatment response and a lower remission rate (Novick et al., 2013a). In addition, some reports have indicated that the resolution of PPS in the presence of residual symptoms is associated with less risk of impaired functioning (Bair et al., 2003; Romera et al., 2014), and that PPS affects appraisals of cost-effectiveness and cost-utility of antidepressants (Pan et al., 2015).

To the best of our knowledge, the difference between melancholic MDD, which is thought to be a highly homogeneous subtype of MDD, and MDD in connection with PPS has not been investigated. Therefore, we believe that this study involving 100 consecutive Japanese outpatients with melancholic MDD is the first attempt to elucidate both the background factors of PPS in MDD and the influence of PPS on treatment outcomes for melancholic MDD.

2. Methods

2.1. Data

This prospective study was conducted from October 2011 to October 2014. Verbal and written consent was obtained from all patients before the study began. All patients were informed that their personal information would remain strictly confidential, that the obtained data would not be used for anything other than the purposes of the study, and that they would still receive care even if they refused to participate in the study and provide data. The Institutional Review Board of Kyowa Hospital approved this study.

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2.2. Study subjects

The study subjects were patients who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria (American Psychiatric Association, 2000) for melancholic MDD and who were treated as outpatients at a mental clinic in Akita, Japan. For elderly patients, additional inclusion criteria were as follows: a Mini-Mental State Examination score of 26 or higher; no obvious memory impairment; and no obvious impairment in performing activities of daily living. No patient reported having any subjective pain symptoms before they contracted MDD; all pain symptoms appeared after the onset of MDD. A total of 100 consecutive outpatients met the above criteria and were included in the study. At initial evaluation (baseline), all patients were interviewed for DSM-IV-TR Axis 2, 3, and 4 and family history of MDD (at least one affected first- or second-degree relative).

2.3. Measurements

In accordance with previous reports (Bair et al., 2003; Ohayon and Schatzberg, 2003), we defined PPS in the present study as follows: (1) existence of a current episode of MDD according to DSM-IV-TR; (2) a physical symptom occurring after the onset of MDD; and (3) a physical symptom in conjunction with joint/articular pain, heaviness of the limbs, back pain, headache, or gastrodynia.

Medication for MDD was prescribed according to the treatment algorithm for MDD developed by Shioe et al. (2003). This treatment includes the use of a selective serotonin reuptake inhibitor (SSRI) as the first-choice drug (Step 1). If remission was not achieved, a stepwise progression from an SSRI to a serotonin-noradrenaline reuptake inhibitor (SNRI) as the second-choice drug (Step 2) was applied. A noradrenergic and specific serotonergic antidepressant (NaSSA), a tetracyclic antidepressant, or sulpiride was chosen as a third-choice drug (Step 3), and a tricyclic antidepressant (TCA) as a fourth-choice drug (Step 4). Antidepressants were used as monotherapy in all steps of treatment.

MDD was evaluated using the 17-item Hamilton Depression Rating Scale (HDRS-17) (Hamilton, 1960), which was measured at baseline and after 12, 24, and 36 weeks of treatment. MDD remission was defined as follows: (1) a total HDRS-17 score of 7 or lower; (2) did not meet the diagnostic criteria for MDD regardless of whether depressive symptoms remained; (3) no dysfunction, domestically or occupationally, in daily life; and (4) the first three conditions are maintained for more than eight weeks.

Each patient was asked about the presence or absence of PPS, as described in a report by Shimodera et al. (2012). PPS were evaluated after 12, 24, and 36 weeks of drug treatment using the following 5-point Likert scale: 0 (unaware of PPS); 1 (slightly aware); 2 (somewhat aware); 3 (moderately aware); and 4 (extremely aware). A score of 0 was defined as PPS remission, and a score of 1 or higher was defined as PPS non-remission.

2.4. Statistical analysis

For data analysis, we used PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). Patients were divided into PPS-positive (PPS+) and PPS-negative (PPS-) groups. Each factor, including DSM-IV-TR Axis 3 and 4 and family history of MDD, was then analyzed for differences between the groups using the *t*-test or the chi-square test. The significance level was set to $p < 0.05$. The mean HDRS-17 scores at baseline and after 12, 24, and 36 weeks of treatment were analyzed in both groups using analysis of variance (ANOVA). Post-hoc analysis (Bonferroni method) was performed to control for multiple comparisons, with the significance level set to $p < 0.05$. To investigate the association between the MDD and PPS remission, and between the timing associated with PPS and MDD remission, we calculated the phi coefficient and Cramer's V, respectively.

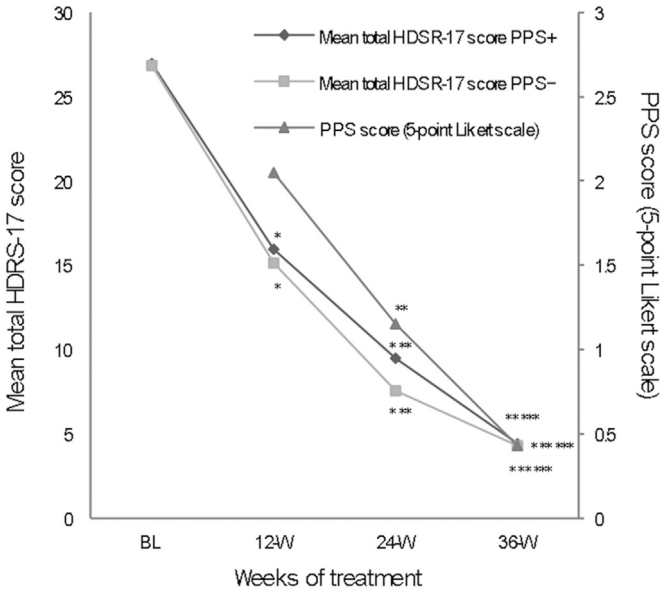

Fig. 1. Mean HDRS-17 scores in the PPS+ and PPS- groups, and PPS scores in the PPS+ group, which were based on a 5-point Likert scale, for each evaluation period. HDRS, Hamilton Depression Rating Scale; PPS, painful physical symptoms; PPS+, painful physical symptom-positive; PPS-, painful physical symptom-negative; BL, baseline = initial evaluation period; 12-W, after 12 weeks of treatment; 24-W, after 24 weeks of treatment; 36-W, after 36 weeks of treatment. $^{*}p < 0.05$ vs BL; $^{**}p < 0.05$ vs 12-W; $^{***}p < 0.05$ vs 24-W.

Regarding antidepressant treatment, we first examined the relationship between PPS and MDD remission. We then investigated differences in responsiveness to each step of antidepressant treatment between the PPS+ and PPS- groups using the chi-square test. In addition, we investigated differences in responsiveness to duloxetine and milnacipran, the SNRIs chosen as second-choice drugs, using the chi-square test (Fig. 1).

3. Results

MDD patients with PPS complained of omalgia, headache, and gastrodynia in decreasing order, consistent with the results reported by Shimodera et al. (2012).

The demographic characteristics of the subjects and the results of interviews regarding DSM-IV-TR Axis 2, 3, and 4 and family history of MDD are shown in Table 1. No significant differences were found between elderly and younger patients ($\chi^2_{(1)}=0.0058$, $p=1.0000$) or between male and female patients ($\chi^2_{(1)}=0.0559$, $p=1.0000$). None of the patients had an Axis 2 disorder. Considering a possible association between metabolic syndrome and depression (Zhang et al., 2005; McIntyre et al., 2009; Pan et al., 2012), attention was paid to coexisting medical conditions such as hypertension, diabetes, and hyperlipidemia associated with Axis 3. "Other illnesses" included arrhythmia and gastrointestinal disturbances. 43% of the patients had no coexisting medical conditions associated with Axis 3. The number of patients who had "none" on Axis 4 was highest. No significant differences were observed in relation to Axis 3 ($\chi^2_{(1)}=1.7892$, $p=0.2166$) or Axis 4 ($\chi^2_{(1)}=0.6866$, $p=0.4823$) between the PPS+ and PPS- groups. A significant difference was found between the PPS+ and PPS- groups in family history of MDD ($\chi^2_{(1)}=5.0581$, $p=0.0327$). No significant differences were found between the PPS+ and PPS-