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ORIGINAL RESEARCH

Residual symptoms in patients with partial versus complete remission of a major depressive disorder episode: patterns of painful physical symptoms in depression

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Objective: The patterns of residual painful physical symptoms (PPS) and emotional symptoms among patients with partial remission (PR) or complete remission (CR) of a major depressive disorder (MDD) episode were compared.

Methods: This is a multicenter, cross-sectional, observational study. Patients who had originally been diagnosed with MDD, were treated with an antidepressant for 12 weeks for that episode, and achieved either PR or CR at study entry were enrolled in the study. Using the 17-item Hamilton Rating Scale for Depression (HAM-D17), PR was defined as a score of ≥8 and ≤18 and CR as a score of ≤7. Residual symptoms were assessed using the Brief Pain Inventory-Short Form (BPI-SF) and the HAM-D17.

Results: A total of 323 patients (CR =158, PR =165) were included in the study. Patients in the PR group had a higher mean (standard deviation) score in the HAM-D17 than those in the CR group (11.8 [3.1] and 4.4 [2.0], respectively). BPI-SF results showed that "at least moderate PPS" (score ≥3 on BPI-SF question 5) was significantly more prevalent among patients with PR than those with CR (37.0% vs 16.5%, respectively; odds ratio =3.04; $P<0.001$). Presence of pain (any severity) was also more prevalent among patients with PR than those with CR (54.5% vs 35.4%, respectively). The HAM-D17 results for individual items indicated that impaired work and activities, depressed mood, psychological and somatic anxiety, and general somatic symptoms were observed in at least 75% of patients with PR.

Conclusion: PR was associated with a higher prevalence of at least moderate PPS. Other residual symptoms commonly observed in patients with PR included typical core emotional symptoms (eg, loss of interest, depressed mood, and psychological anxiety). These results underline the importance of PPS, because PPS is clinically relevant for the patients but difficult to assess with the commonly used depression evaluation scale.

Keywords: major depressive disorder, residual symptoms, partial remission, complete remission, painful physical symptoms, pain, depression

Introduction

Major depressive disorder (MDD) encompasses a broad range of emotional and physical symptoms.[1] The optimal goal in the treatment of patients with MDD should be the complete remission (CR) of symptoms and a return to the same functionality level experienced prior to the episode.[2] However, it is known that approximately one-third of patients experience only partial remission (PR), experiencing insufficient improvement and persistent residual symptoms.[3,4] PR is characterized by the presence of residual

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symptoms that heavily impact depression prognosis. Judd et al[5] reported that patients who experienced MDD with residual symptoms relapsed more than three times faster than those without. Those symptoms were also found to be a predictor of nonrecovery from depression.[5]

A clinical pattern of residual symptoms has been reported by Paykel et al[6] using the rating scale of the 17-item Hamilton Rating Scale for Depression (HAM-D17). In their study, patients often gave a positive response to the general somatic symptoms item, along with other items related to more typical depressive symptoms, such as depressed mood, impairment of work and interests, and psychological anxiety.[6] However, because the general somatic symptoms item on the HAM-D17 refers to both nonpainful physical symptoms (non-PPS; eg, loss of energy and fatigability) and painful physical symptoms (PPS; eg, backaches, headache, and muscle aches) and does not distinguish one from the other, the prevalence of PPS as a residual symptom has remained unclear. From a clinical perspective, PPS in patients with depression are known to worsen patients' prognosis. For example, the presence of pain slowed treatment progression and was predictive of an increased time to remission,[7] but little emphasis has been placed on the presence of PPS as part of a pattern of residual symptoms.

Therefore, we aimed to assess the pattern of residual PPS, hypothesizing that PPS of at least moderate severity would be more prevalent among patients with PR than patients with CR.

Methods

Study design

This was a multicenter, cross-sectional, observational study conducted at 27 psychiatry and psychosomatic outpatient clinics in Japan. Patients with PR or CR after 12 weeks of treatment were enrolled and underwent pair-wise matching by age and sex: two strata for sex (male and female) and three strata for age (20–39, 40–65, and ≥66 years). The number of patients with PR and CR in each age and sex stratum was as equal as possible.

Study population

Patients ≥20 years old who had originally been diagnosed with MDD without psychotic features, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision,[1] were treated with an antidepressant for 12 weeks (±3 weeks) for that episode, and achieved either PR or CR at study entry were eligible for enrollment in the study. The diagnosis of the MDD episode was made by the investigators in normal clinical settings. PR was defined as an HAM-D17 score of ≥8 and ≤18,[6] and CR was defined as an HAM-D17 score of ≤7.[8] The antidepressant treatment regimen prior to and after enrollment was at the sole discretion of the physician and the patient, according to usual standard of care. Patients were excluded if they had a previous diagnosis of bipolar disorder, schizophrenia, or other psychotic disorder; had a current diagnosis of dysthymic disorder or adjustment disorder; or had an HAM-D17 score ≥19.

Ethics

This study was reviewed and approved by the applicable institutional ethical review boards and was conducted in accordance with applicable laws and regulations of Japan, as appropriate. All patients provided written informed consent after they were given an explanation of the study and prior to enrollment and data collection. The confidential nature of patient information was maintained. The investigators or appointed personnel entered data in electronic data collection application, and the investigators validated the data for correctness with a written signature.

Study assessments

The Brief Pain Inventory-Short Form (BPI-SF) questionnaire was used to assess PPS. Question (Q)1 reveals the presence of pain of any severity (referred to as "any pain" or "any severity of pain" hereafter) and Q2 identifies the location of pain (body site). Q3 through Q6 assess the intensity of worst, least, average, and current pain, respectively. A score of ≥3 on Q5 (average pain) is considered at least moderate severity of pain (referred to as "at least moderate PPS" hereafter).[9] Q8 evaluates how much relief pain treatments or medications have provided. Q9 assesses how much pain interferes with daily activities in various forms. For Q3–Q6 and Q9, two populations were analyzed: all patients (including the patients who reported no pain; ie, those who answered "no" on Q1) and the pain-positive subgroup (only the patients who reported any pain; ie, those who answered "yes" on Q1).

The HAM-D17 is a 17-item, clinician-rated scale used to assess the severity of depression and its improvement.[8,10] Item score ranges in this scale are 0–2 or 0–4. Residual symptoms at the time of enrollment were regarded as present when the score on each item of the HAM-D17 was ≥1. In addition, residual symptoms were grouped into mild (score of 1) and moderate or higher (scores of 2–4), as defined in the study by Paykel et al.[6] The Structured Interview Guide for the Hamilton Depression Rating Scale was also used in this study.[11–13]

The Social and Occupational Functioning Assessment Scale (SOFAS), a 100-point single-item scale, was used to indicate the individual's level of social and occupational

functioning across a continuum ranging from a state of optimal functioning to a state of grossly impaired functioning.[14] An SOFAS score ≥80 was defined as normal levels of functionality.[15]

Clinicians assessed and categorized patients' treatment adherence by asking whether the patients were taking the medicine: 1) exactly as prescribed (100%); 2) most of the time (76%–99%); 3) slightly less than prescribed (50%–75%); or 4) significantly less than prescribed (<50%). No data regarding precise individual antidepressant dosing were collected. Sociodemographic parameters were also collected.

Statistical analysis

All patients who provided consent to release information and who fulfilled the study entry criteria were included in all of the analyses. A logistic regression model was used for the endpoint analysis. The model included a prevalence of at least moderate PPS as a response variable; group (CR and PR), sex (female and male), and age (category by 10 years) were treated as explanatory variables. In addition, comparisons using Fisher's exact test were also made between the groups, overall and by sites where at least moderate PPS were experienced. Each component of the BPI-SF was also summarized and compared between the CR and PR subgroups. Each item of the HAM-D17 was compared using a two-sample *t*-test. Due to the observational nature of this study, covariate adjustments were made to control for biases and confounding factors in the logistic regression model. Although age and sex were used as matching factors, they were also included in the analysis model to decrease the data variation and the potential bias due to the imbalance of these factors between groups. All of the statistical tests were based on a two-sided significance level of 0.05, unless otherwise specified.

Results

Patient characteristics

A total of 323 patients (CR =158 [48.9%], PR =165 [51.1%]) were included in the study. Mean patient age was 46.2 years, and 52.0% of patients were women (Tables 1 and 2). Mean age at the onset of the first depressive episode was 41.5 years, with a mean of 1.5 previous MDD episodes and a mean total duration of 33.8 weeks for the current MDD episode. Physical

Table 1 Sociodemographic characteristics

Variables	Total	CR group	PR group
n	323	158	165
Age (years)			
≥20–<40, n (%)	116 (35.9)	51 (32.3)	65 (39.4)
≥40–<66, n (%)	165 (51.1)	84 (53.2)	81 (49.1)
≥66, n (%)	42 (13.0)	23 (14.6)	19 (11.5)
Mean ± SD	46.2±14.8	47.7±14.9	44.8±14.7
Min, max	20, 81	20, 81	20, 81
Sex			
Male, n (%)	155 (48.0)	78 (49.4)	77 (46.7)
Age (years), n (%)			
≥20–<40	55 (35.5)	27 (34.6)	28 (36.4)
≥40–<66	87 (56.1)	44 (56.4)	43 (55.8)
≥66	13 (8.4)	7 (9.0)	6 (7.8)
Sex			
Female, n (%)	168 (52.0)	80 (50.6)	88 (53.3)
Age (years), n (%)			
≥20–<40	61 (36.3)	24 (30.0)	37 (42.0)
≥40–<66	78 (46.4)	40 (50.0)	38 (43.2)
≥66	29 (17.3)	16 (20.0)	13 (14.8)
Educational background, n (%)			
Junior high school or lower	27 (8.4)	13 (8.2)	14 (8.5)
High school or vocational school	155 (48.0)	74 (46.8)	81 (49.1)
College degree or higher	141 (43.7)	71 (44.9)	70 (42.4)
Current work status, n (%)			
Part-time worker	30 (9.3)	13 (8.2)	17 (10.3)
Full-time worker	157 (48.6)	72 (45.6)	85 (51.5)
Self-employed worker	15 (4.6)	11 (7.0)	4 (2.4)
Student	5 (1.5)	3 (1.9)	2 (1.2)
Housewife	62 (19.2)	37 (23.4)	25 (15.2)
Unemployed due to reasons other than current disorder (MDD)	11 (3.4)	5 (3.2)	6 (3.6)
Unemployed due to current disorder (MDD)	18 (5.6)	4 (2.5)	14 (8.5)
Post-retirement	25 (7.7)	13 (8.2)	12 (7.3)

Abbreviations: CR, complete remission; Max, maximum; MDD, major depressive disorder; Min, minimum; PR, partial remission; SD, standard deviation.

Table 2 Clinical characteristics

Variables	Total	CR group	PR group
n	323	158	165
Age at first depressive episode (years)			
n[a]	297	146	151
Mean ± SD	41.5±14.7	43.1±15.6	40.0±13.7
Number of previous depressive episodes			
n[a]	223	109	114
Mean ± SD	1.5±1.0	1.6±1.1	1.5±0.9
Total duration of the current episode of MDD (weeks)			
n	323	158	165
Mean ± SD	33.8±56.9	31.4±63.9	36.0±49.4
Previous diagnosis of personality disorders, n (%)			
No	318 (98.5)	157 (99.4)	161 (97.6)
Yes	3 (0.9)	1 (0.6)	2 (1.2)
Unknown	2 (0.6)	0 (0.0)	2 (1.2)
Alcohol intake condition, n (%)			
Yes	101 (31.3)	48 (30.4)	53 (32.1)
HAM-D17 total score			
n	323	158	165
Mean ± SD	8.2±4.5	4.4±2.0	11.8±3.1
SOFAS			
n[a]	298	145	153
≥80, n (%)	67 (22.5)	62 (42.8)	5 (3.3)
Mean ± SD	67.0±13.7	75.5±10.7	58.9±11.3
Presence of physical comorbidities that may cause PPS, n (%)			
No	281 (87.0)	138 (87.3)	143 (86.7)
Yes	32 (9.9)	14 (8.9)	18 (10.9)
Unknown	10 (3.1)	6 (3.8)	4 (2.4)
Hospitalization, n (%)			
Yes	4 (1.2)	3 (1.9)	1 (0.6)
Early retirement, n (%)			
Yes	12 (3.7)	2 (1.3)	10 (6.1)
Sick leave, n (%)			
Yes	103 (31.9)	39 (24.7)	64 (38.8)
Antidepressants, n (%)			
SSRI	147 (45.5)	75 (47.5)	72 (43.6)
SNRI	118 (36.5)	59 (37.3)	59 (35.8)
Tricyclic	24 (7.4)	10 (6.3)	14 (8.5)
Tetracyclic	4 (1.2)	1 (0.6)	3 (1.8)
Others	32 (9.9)	14 (8.9)	18 (10.9)
Antidepressant compliance, n (%)[b]			
100%	254 (78.6)	127 (80.4)	127 (77.0)
76%–99%	61 (18.9)	28 (17.7)	33 (20.0)
50%–75%	5 (1.5)	1 (0.6)	4 (2.4)
<50%	3 (0.9)	2 (1.3)	1 (0.6)
Analgesic treatment and classes, n (%)			
Yes	64 (19.8)	20 (12.7)	44 (26.7)
NSAIDs[c]	63 (98.4)	20 (100.0)	43 (97.7)
Nonopioid[c]	1 (1.6)	0 (0.0)	1 (2.3)
Benzodiazepine treatment and purpose of use, n (%)			
Yes	245 (75.9)	106 (67.1)	139 (84.2)
Insomnia[c]	142 (58.0)	55 (51.9)	87 (62.6)
Anxiety[c]	167 (68.2)	66 (62.3)	101 (72.7)
Other[c]	15 (6.1)	6 (5.7)	9 (6.5)
Intensive psychotherapy[d], n (%)			
Yes	159 (49.2)	77 (48.7)	82 (49.7)

Notes: [a]The number of the patients whose data was available. [b]P=0.4403 (group comparison between the CR and PR groups, conducted using the Mann–Whitney–Wilcoxon test). [c]Percentage is calculated by using the number of patients who answered "Yes" as the denominator. [d]Intensive psychotherapy includes cognitive behavioral therapy, group psychotherapy, and psychoanalysis.

Abbreviations: CR, complete remission; HAM-D17, 17-item Hamilton Rating Scale for Depression; MDD, major depressive disorder; NSAIDs, nonsteroidal anti-inflammatory drugs; PPS, painful physical symptoms; PR, partial remission; SD, standard deviation; SNRI, serotonin norepinephrine reuptake inhibitor; SOFAS, Social and Occupational Functioning Assessment Scale; SSRI, selective serotonin reuptake inhibitor.

comorbidities with the potential to cause PPS were present in 9.9% of patients. Sociodemographic variables, including age, sex, educational background, and current work status, were similar between groups (Table 1). Most clinical variables were also similar between groups, but patients in the PR group had, by definition, a higher mean (standard deviation) score in the HAM-D17 than those in the CR group (11.8 [3.1] and 4.4 [2.0], respectively). In addition, the mean (standard deviation) SOFAS score was higher for the CR group than the PR group (75.5 [10.7] and 58.9 [11.3], respectively). Similarly, the proportion of patients achieving SOFAS score of ≥80 was higher for the CR group than the PR group (43% and 3%, respectively).

Treatment pattern and adherence

All patients had received acute antidepressant treatment for approximately 3 months prior to this study. Most patients were treated with selective serotonin reuptake inhibitors (45.5%) or selective serotonin and noradrenalin reuptake inhibitors (36.5%); the distribution of antidepressant classes was similar between patients with CR and PR (Table 2). Overall, 78.6% of patients took antidepressants "exactly as prescribed (100%)" and 18.9% of patients did so "most of the time (76%–99%)". Differences in treatment compliance between groups were not statistically significant (Table 2). Concomitant medication use is also presented in Table 2. Patients with PR received more nonsteroidal anti-inflammatory drugs (26.7% vs 12.7%, respectively) and benzodiazepine treatment (84.2% vs 67.1%, respectively) compared to patients with CR. Approximately 50% of patients in each group received psychotherapy (eg, cognitive behavioral therapy, group psychotherapy, psychoanalysis) (Table 2).

Individual residual symptoms

The prevalence of at least moderate PPS in the PR group was significantly higher than that in the CR group (37.0% vs 16.5%, respectively; $P<0.001$). As described above, logistic regression analysis included the prevalence of at least moderate PPS as a response variable and group (CR and PR), sex, and age as explanatory variables. Using logistic regression, the prevalence of at least moderate PPS in the PR group was significantly higher than that in CR group (odds ratio =3.04; 95% confidence interval [CI] =1.78–5.18; $P<0.001$) (Table 3). The prevalence of PPS among female patients was numerically higher than among male patients, but this was not statistically significant (odds ratio =1.61; 95% CI =0.96–2.70). There appeared to be no significant effect of age (Table 3).

BPI-SF results are shown in Table S1. Overall, 45.2% of patients experienced pain symptoms, with head (10.8%), neck (7.1%), shoulder (5.6%), lower back (5.3%), and back (4.0%) being the most commonly reported locations of pain. Patients with PR were more likely to experience pain than patients with CR (54.5% vs 35.4%, respectively), although the body locations that hurt most were similar between groups. Pain sites that were seen in more than 10% of patients with PR were the head (15.2%) and neck (10.3%), which were more than twice that of the CR group (Table S1).

Table 3 Odds ratios associated with prevalence of residual symptoms, "at least moderate PPS", defined as a BPI-SF average pain score of 3 or greater

Explanatory variables	Odds ratio	95% CI	*P*-values
Group (CR: 0, PR: 1)	3.04	1.78–5.18	<0.001
Sex (male: 0, female: 1)	1.61	0.96–2.70	0.070
Age (category by 10 years)	1.06	0.90–1.26	0.49

Notes: Logistic regression was used. The base variable was 0 and the evaluation variable was 1.
Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; CR, complete remission; PPS, painful physical symptoms; PR, partial remission.

The degree of worst, least, average, and current pain was higher in the PR group than in the CR group, and a smaller difference was seen in the pain-positive subgroup. Daily activities of the PR group were generally more disrupted than those of the CR group in both the all-patients population and the pain-positive subgroup. Among the pain-positive subgroups, interference with daily activities for the PR group was especially high for enjoyment of life, mood, and normal work.

The mean and distribution of scores on each item of the HAM-D17 are shown in Table S2. Patients with CR had lower scores across all items of the HAM-D17, compared to patients with PR. The same trend also applied to the frequency of residual symptoms for each HAM-D17 item. The symptoms present were typical core symptoms of depression. The most frequently observed residual symptoms (more than 75%) among patients with PR were work and activities (97.6%), depressed mood (95.8%), psychological anxiety (86.7%), somatic anxiety (81.8%), and general somatic symptoms (78.2%). The same order of frequency was observed for moderate or higher scores (scores of 2–4) for each item: work and activities (64.2%), depressed mood (64.2%), psychological anxiety (35.2%), somatic anxiety (26.1%), and general somatic symptoms (18.2%). The remaining symptoms were present, to at least a mild degree, in 20% of the patients with PR, with the exceptions of loss of weight and insight. The same top five residual symptoms were also common in patients with CR: work and activities (63.9%), depressed mood (53.2%), general somatic symptoms (46.2%), psychological anxiety (43.0%), and somatic anxiety (41.1%).

Discussion

The results presented here demonstrate that at least moderate residual PPS are more prevalent among patients with PR than those with CR after antidepressant treatment. Furthermore, our results revealed the details of residual PPS, which are clinically relevant to patients, but are difficult to assess in the commonly used depression scale. For example, HAM-D item 13 "general somatic symptoms" assesses both non-PPS and PPS and does not distinguish one from the other. The frequencies of general somatic symptoms (indicated by a HAM-D item 13 score ≥1), any pain (indicated by BPI-SF Q1 answer of yes), and at least moderate pain (indicated by a BPI-SF Q5 score ≥3) were 78.2%, 54.5%, and 37.0%, respectively, in the PR group and 46.2%, 35.4%, and 16.5%, respectively, in the CR group. Therefore, we may assume that among those with residual somatic symptoms, approximately three-quarters of patients have some pain, and this is consistent across patients with PR and CR. Similarly, regarding the severity of pain, about two-thirds of the pain symptoms among patients with PR and approximately half of the pain symptoms among patients with CR were of at least moderate severity. These results suggest that both frequency and severity of pain are higher among patients with PR compared to those with CR. This clinical perspective will help clinicians to accurately and thoroughly assess and treat residual physical symptoms from which patients with MDD suffer.

This study reinforces and advances our understanding of the nature of residual symptoms. We have shown that core emotional symptoms in MDD, such as impaired work and activities, depressed mood, and psychological anxiety, were highly prevalent among patients with PR and to a lesser extent among patients with CR. In addition, this study has shown that physical symptoms, represented by general somatic symptoms, may have been overlooked by doctors and patients, but were actually common residual symptoms, following the core emotional symptoms in prevalence.

Paykel et al[6] reported in their study that residual symptoms were a combination of typical core depressive symptoms with both emotional and physical symptoms. Our study supports this finding, providing more detailed information on PPS as a pattern of residual symptoms. Regarding the location of pain, the head, neck, and shoulder pain were very common, and this is consistent with other studies.[16,17] Furthermore, the fact that patients with PR exhibited more head and neck pain may indicate an increased risk of migraine and tension-type headaches as a secondary effect of MDD.[18,19]

Limitations

There are several limitations to our study. Firstly, because this was an observational study, one cannot infer causality between PR and the presence of PPS, but rather only an association between the two. Secondly, at the time of enrollment, patients had been treated for 12 weeks and no information was collected at treatment initiation. Therefore, it was difficult to match the patients with PR and CR according to the severity of the depressive symptoms, backgrounds, or PPS at the initiation of treatment. Thirdly, only patients who continued treatment for 12 weeks were recruited for the study; therefore, those who discontinued early were not included. However, due to the naturalistic design of the study, both cohorts reflected the reality of a typical clinical setting. In addition, to minimize the effect of confounders, patients were matched for age and sex. Similarity in social and clinical backgrounds, including the duration of current MDD episode, may have helped to ensure similarity in MDD episode severity at onset. Because patients were included in the study during the course of an MDD episode, information regarding the BPI-SF, HAM-D17, SOFAS, and other relevant information at the onset of the episode was not collected. Fourthly, we did not assess symptom improvement from the beginning of treatment (ie, before our study). We assessed it only at baseline (ie, approximately 12 weeks after drug initiation). Only the baseline HAM-D17 scores were used to define CR/PR. However, the diagnosis of MDD was made by the investigator according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision criteria, though not necessarily using a structured interview guide. Lastly, we have not analyzed each antidepressant's impact on PPS, since our objective was to provide details on residual symptoms using a noninterventional, cross-sectional design. Assessment of efficacy of antidepressants on PPS was out of the scope of the study.

Conclusion

In summary, MDD presents with various residual symptoms, including typical core depressive symptoms and PPS. Our results contribute to a better understanding of the pattern of residual PPS in patients with depression. Our findings underline the importance of PPS, because PPS is clinically relevant for the patients but difficult to assess in the commonly used depression evaluation.

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Author contributions

All authors participated in the interpretation of the data, drafting, critical revision, and approval of the final version of the manuscript.

Disclosure

EH contributed to this work as a former full-time employee of Eli Lilly Japan K.K.. The opinions expressed in this work are solely his and do not represent his current affiliation, that is, the Japanese Ministry of Health, Labour and Welfare.

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Supplementary materials

Table S1 BPI-SF components

BPI-SF question			Total	CR group	PR group
n			323	158	165
n (%)					
Q1	Presence of pain	Yes	146 (45.2)	56 (35.4)	90 (54.5)
Q2	Site that hurts the most	Head	35 (10.8)	10 (6.3)	25 (15.2)
		Neck	23 (7.1)	6 (3.8)	17 (10.3)
		Shoulder	18 (5.6)	9 (5.7)	9 (5.5)
		Lower back	17 (5.3)	8 (5.1)	9 (5.5)
		Back	13 (4.0)	6 (3.8)	7 (4.2)
		Lower limb	10 (3.1)	5 (3.2)	5 (3.0)
		Chest	8 (2.5)	5 (3.2)	3 (1.8)
		Stomach	7 (2.2)	2 (1.3)	5 (3.0)
		Upper limb	6 (1.9)	1 (0.6)	5 (3.0)
		Joint	5 (1.5)	2 (1.3)	3 (1.8)
		Oral cavity	3 (0.9)	2 (1.3)	1 (0.6)
		Face	1 (0.3)	0 (0.0)	1 (0.6)
		Urogenital apparatus	0 (0.0)	0 (0.0)	0 (0.0)
Score (mean ± SD)					
			All patients[a]/subgroup[b]	**All patients[a]/subgroup[b]**	**All patients[a]/subgroup[b]**
Q3	Pain intensity	Worst	2.1±2.6/4.6±2.0	1.6±2.4/4.4±2.0	2.6±2.7/4.7±1.9
Q4	in past 24	Least	0.7±1.2/1.5±1.4	0.5±1.1/1.4±1.4	0.9±1.3/1.6±1.5
Q5	hours	Average	1.3±1.8/3.0±1.5	0.9±1.5/2.6±1.4	1.7±2.0/3.2±1.6
Q6	Current level of pain-related distress		1.2±1.7/2.7±1.7	0.8±1.4/2.3±1.4	1.6±2.0/2.9±1.8
Q8[c]	Level of pain relief from medications		1.5±2.7[d]/3.5±3.2[e]	1.2±2.5[f]/3.6±3.3[g]	1.9±2.9[h]/3.5±3.1[i]
Q9 (average)	Interference with daily activities		0.88±1.45/1.94±1.61	0.44±0.93/1.25±1.21	1.29±1.71/2.37±1.68
	Q9A	General activity	1.2±1.8/2.6±1.8	0.8±1.4/2.1±1.6	1.6±2.0/2.8±1.9
	Q9B	Mood	1.1±1.8/2.5±2.0	0.5±1.2/1.5±1.6	1.7±2.1/3.1±1.9
	Q9C	Walking ability	0.4±1.4/0.9±1.9	0.2±0.9/0.6±1.4	0.6±1.7/1.0±2.2
	Q9D	Normal work	1.1±1.9/2.4±2.2	0.5±1.2/1.5±1.6	1.6±2.3/3.0±2.4
	Q9E	Relations with other people	0.6±1.4/1.3±1.9	0.2±0.8/0.5±1.2	1.0±1.7/1.8±2.0
	Q9F	Sleep	0.5±1.3/1.2±1.8	0.3±0.9/0.8±1.3	0.8±1.6/1.5±2.0
	Q9G	Enjoyment of life	1.2±2.1/2.7±2.3	0.6±1.2/1.6±1.6	1.9±2.5/3.4±2.4

Notes: For Q3–Q6, Q8, and Q9, item scores on this scale range between 0 and 10. Q7 (What treatments or medications are you receiving for your pain?): not evaluated in this study. [a]If the answer for Q1 was "no" (had no pain), the score was entered as 0. [b]Only patients who had pain (answered "yes" on Q1) were included. [c]Q8: The original scale of BPI-SF (0%–100%) was replaced with a score of 0–10 in this study. [d]n=312; [e]n=135; [f]n=153; [g]n=51; [h]n=159; [i]n=84.

Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; CR, complete remission; PR, partial remission; SD, standard deviation.

Table S2 Distribution of rating and mean scores on each HAM-D17 item

Item/symptoms	CR group n=158				PR group n=165				*P*-values[a]
	Score, n (%)			Mean scores	Score, n (%)			Mean scores	
	0	1	2–4		0	1	2–4		
1 Depressed mood	74 (46.8)	74 (46.8)	10 (6.3)	0.6	7 (4.2)	52 (31.5)	106 (64.2)	1.8	<0.001
2 Guilt	129 (81.6)	29 (18.4)	0 (0.0)	0.2	87 (52.7)	68 (41.2)	10 (6.1)	0.5	<0.001
3 Suicide	153 (96.8)	4 (2.5)	1 (0.6)	0.0	130 (78.8)	31 (18.8)	4 (2.4)	0.2	<0.001
4 Insomnia early	126 (79.7)	32 (20.3)	0 (0.0)	0.2	94 (57.0)	54 (32.7)	17 (10.3)	0.5	<0.001
5 Insomnia middle	128 (81.0)	30 (19.0)	0 (0.0)	0.2	84 (50.9)	72 (43.6)	9 (5.5)	0.5	<0.001
6 Insomnia late	142 (89.9)	12 (7.6)	4 (2.5)	0.1	109 (66.1)	52 (31.5)	4 (2.4)	0.4	<0.001
7 Work and activities	57 (36.1)	86 (54.4)	15 (9.5)	0.8	4 (2.4)	55 (33.3)	106 (64.2)	2.0	<0.001
8 Psychomotor retardation	148 (93.7)	10 (6.3)	0 (0.0)	0.1	106 (64.2)	54 (32.7)	5 (3.0)	0.4	<0.001
9 Psychomotor agitation	148 (93.7)	10 (6.3)	0 (0.0)	0.1	132 (80.0)	29 (17.6)	4 (2.4)	0.2	<0.001
10 Psychological anxiety	90 (57.0)	59 (37.3)	9 (5.7)	0.5	22 (13.3)	85 (51.5)	58 (35.2)	1.3	<0.001
11 Somatic anxiety	93 (58.9)	56 (35.4)	9 (5.7)	0.5	30 (18.2)	92 (55.8)	43 (26.1)	1.1	<0.001
12 Loss of appetite (gastrointestinal somatic symptoms)	141 (89.2)	17 (10.8)	0 (0.0)	0.1	102 (61.8)	59 (35.8)	4 (2.4)	0.4	<0.001
13 General somatic symptoms	85 (53.8)	64 (40.5)	9 (5.7)	0.5	36 (21.8)	99 (60.0)	30 (18.2)	1.0	<0.001
14 Sexual interest (genital symptoms)	133 (84.2)	23 (14.6)	2 (1.3)	0.2	88 (53.3)	65 (39.4)	12 (7.3)	0.5	<0.001
15 Hypochondriasis	127 (80.4)	28 (17.7)	3 (1.9)	0.2	96 (58.2)	55 (33.3)	14 (8.5)	0.5	<0.001
16 Loss of weight	150 (94.9)	6 (3.8)	2 (1.3)	0.1	135 (81.8)	20 (12.1)	10 (6.1)	0.2	<0.001
17 Insight	147 (93.0)	11 (7.0)	0 (0.0)	0.1	140 (84.8)	25 (15.2)	0 (0.0)	0.2	0.019

Notes: [a]*P*-values for the differences between mean scores in the CR and PR groups. The statistical test was conducted using 2-sample *t*-test.
Abbreviations: CR, complete remission; HAM-D17, 17-item Hamilton Rating Scale for Depression; PR, partial remission.