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# The frequency and severity of symptoms of major depression in Chinese patients with chronic, medically unexplained, painful physical symptoms who present to a general neurology clinic

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### *Abstract*

This cross-sectional, non-interventional, observational study evaluated depression in patients in China who presented to a general neurologist with chronic, medically unexplained, painful physical symptoms. Of the 402 patients enrolled, 197 patients (49.0%) met the criteria for a current major depressive episode (MDE+ group), as assessed using module A of the Mini International Neuropsychiatric Interview, and 205 patients (51.0%) did not (MDE- group). The mean pain severity visual analogue scale (VAS) score was significantly higher in the MDE+ group than the MDE- group (65.3 vs 55.6 mm; $p<0.001$). The mean depression severity score, as assessed using the 9-item Patient Health Questionnaire (PHQ-9), was 8.4 units (95% CI: 7.3 to 9.5) higher in the MDE+ group than the MDE- group (mean PHQ-9 total score: 14.8 vs 6.4). Anxiety and perceived health state were significantly worse, on average, in the MDE+ group (mean Hospital Anxiety and Depression Scale anxiety subscale score 10.7 vs 5.9 units; mean EuroQoL-5 Dimensions VAS score 56.4 vs 67.7 mm; each $p<0.001$). Only 14.2% of patients had received treatment for depression during the past 3 months. These results suggest depression was common and may have been under-treated in this group of Chinese patients with chronic, medically unexplained painful physical symptoms.

## INTRODUCTION

Major depressive disorder (MDD) is one of the most common psychiatric disorders and is associated with significant long-term disability.[1] As well as psychological, behavioral, and emotional symptoms, patients with MDD often experience painful physical symptoms (PPS) that do not have a clear medical explanation.[2,3] These patients frequently present at primary care clinics with PPS only, and their depression may go undiagnosed and untreated.[4,5] Studies in different clinical settings (primary care, psychiatric, and neurology clinics) have shown that depression is associated with an increased risk of chronic pain and, conversely, chronic pain is associated with an increased risk of depression.[2,3,6-12] Furthermore, the presence of both chronic pain and depression adversely affects the probability of successful treatment of the individual conditions: concomitant depression increases the morbidity of chronic pain and complicates pain treatment[2,7,10,13,14], and concomitant pain is associated with a more malignant course of depression and a poorer response to treatment.[2,7,11,15-20] In addition, patients with both chronic pain and depression tend to have a poorer quality of life compared with patients with either condition alone.[6,10-12,20,21] Although the pain

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was not explicitly defined in all of these studies, it was most likely pain in the form of medically unexplained PPS. Recognition of the potential for major depression in patients presenting with PPS is therefore important for the optimal treatment of the patient.

Research conducted in different clinical settings, including neurology clinics, highlights the importance of an awareness by physicians of the association between pain and depression. In 2003, Bair et al. published an extensive systematic review of studies that addressed both pain and depression symptoms, which included studies examining specific symptoms of pain as well as general pain.[2] Studies in which patients had pain caused by specific disease processes or syndromes were excluded. This review showed that concomitant depression was common among patients presenting with PPS. The mean (range) prevalence rates of concomitant major depression in patients with pain was 27% (5.9% to 46%) in primary care clinics, 38% (6% to 64%) in psychiatric clinics, and 52% (1.5% to 100%) in pain clinics.[2] In addition, three large studies conducted in neurology clinics in the United States and Europe found that approximately 33% to 50% of newly referred patients (although not necessarily presenting with PPS) had a depressive and/or anxiety disorder.[21-23] These studies illustrate the need for neurologists to consider the possibility of depression in patients presenting with PPS.

Although recent research has shown that PPS are prevalent in Asian patients with MDD in psychiatric settings[11,18,20], less is known about the prevalence of MDD in neurology patients in Asia. In particular, there is little information about the frequency of MDD in patients in China with medically unexplained PPS. The aim of this study was to evaluate the frequency and severity of symptoms of major depression in patients in China who presented to a general neurology clinic with chronic, medically unexplained PPS. The primary objective was to determine the proportion of patients who fulfilled the criteria for a current major depressive episode (MDE) as assessed by the investigators using module A of the Mini-International Neuropsychiatric Interview (MINI). The secondary objectives included: assessment of the overall severity of pain, depression, and anxiety; assessment of health-related quality of life; and investigation of the possible associations between pain, depression, anxiety, and quality of life. Information on the treatment received for pain, depression, and/or anxiety was also collected.

## METHODS

### *Study information*

This was a cross-sectional, non-interventional, observational study (study code: F1J-GH-B032) conducted at 11 general neurology clinics in hospitals in major urban centers in mainland China (Beijing, Chongqing, Changsha, Nanjing, Shanghai, Sichuan, Tianjin, Zhengzhou) between March 2009 and April 2010. The study was conducted in accordance with the Declaration of Helsinki, good clinical practices, and applicable laws and regulations. Approval to conduct the study was received from the participating institutional ethics review boards, and all patients were required to provide written informed consent for the release of their study data before any research-related assessments were conducted.

### *Study population*

Eligible patients were aged ≥18 and <65 years, and had PPS for at least 3 months that did not appear to have a medical explanation or organic cause according to the treating neurologist's clinical judgment. Patients were required to have a sufficient level of understanding and ability to provide informed consent, complete the study assessments, and communicate effectively with the investigator (no cognitive or language impairment). Eligible patients must have signed the written informed consent form before enrollment to confirm that they consented to the release of their data after being informed of the study. Patients had to be able to complete all of the study assessments on the same day. Patients with a known medical condition or organic cause that could explain their PPS (e.g. fibromyalgia, arthritis, rheumatism, diabetic peripheral neuropathy, injury, or surgical wound) were excluded from the study. Participation in another clinical study that involved treatment with an investigational drug or intervention within 30 days of study entry or at the time of the study visit was not allowed.

### *Assessments*

There was no investigational drug or intervention in this study. Treatment initiation and changes were solely at the discretion of the patient, the investigator, and other relevant health care providers. Investigators were instructed to make all treatment decisions for PPS, depression, and any comorbidity based on their usual clinical

practice. No medications were provided by the study sponsor and participation in the study did not influence payment or reimbursement for any treatment received by patients during the study.

There was only one assessment visit for the study; all of the study assessments were completed on the same day. Assessments related to the patients' physical symptoms were required to be completed first, followed by assessments of health-related quality of life and mental health. Patients were provided with a validated Chinese language version of each patient-rated questionnaire and scale.

Investigators used module A of the MINI (version 5.0.0)[24] to determine whether patients met the criteria for a current MDE. This module is a brief, structured, validated checklist that assesses the degree to which nine key symptoms of major depression have affected the patient during the past 2 weeks. Patients rated their overall severity of pain during the past week using a 100 mm visual analogue scale (VAS) from 'No pain' (0 mm) to 'The worst pain I can imagine' (100 mm). Patients rated the degree to which they had been bothered by 28 specific physical symptoms during the past week using the modified Somatic Symptom Inventory (SSI-28), on a scale of 1 ('Not at all') to 5 ('A great deal').[25] The SSI-28 assesses pain-related symptoms at seven sites (muscles, abdomen, lower back, heart or chest, headaches, joints, and neck) and various non-pain-related symptoms (e.g. nausea or vomiting, feeling faint or dizzy, trouble catching your breath). If necessary, patients could receive limited assistance to complete the SSI-28 questionnaire from the investigator or a trained assistant. Patients rated their overall severity of depression during the past 2 weeks using the 9-item Patient Health Questionnaire (PHQ-9).[26] Each of the 9 items was scored from 0 ('Not at all') to 3 ('Nearly every day'). Therefore, PHQ-9 total scores could range from 0 to 27. PHQ-9 scores ≥10 were considered to represent clinically significant depression.[26] The patients' responses to the PHQ-9 were also used to determine whether they met the criteria for MDD. Patients rated their overall severity of anxiety during the past week using the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS).[27] Each of the 7 items on the anxiety subscale was rated against a 4-point rating scale (0 to 3). Therefore, HADS anxiety subscale total scores could range from 0 to 21. The higher the total score, the greater the severity of anxiety experienced by the patient during the past week. Patients rated their current, perceived health state (health-related quality of life) from 0 ('Worst possible health') to 100 ('Best possible health') using the EuroQoL-5 Dimensions vertical visual analogue scale (EQ-5D VAS).[28]

Descriptive information regarding the patients' treatments for pain, depression, and/or anxiety during the past 3 months was collected, including medical (both pharmaceutical and traditional) and physical therapies.

*Statistical analysis*

The primary endpoint was the proportion of patients in the study population who met the criteria for a current MDE and the associated 95% confidence interval (CI). This was calculated by dividing the number of patients who fulfilled the criteria for a current MDE (as assessed using MINI module A) by the total number of eligible patients enrolled in the study. The secondary endpoints included: the pain VAS, SSI-28, PHQ-9, HADS anxiety subscale, and EQ-5D VAS scores; the assessment of the association between the severity of pain and the severity of depression; current treatments used for pain, depression, and/or anxiety; and the concordance between the proportion of patients considered to fulfill the criteria for a current MDE (as assessed by the clinician-rated MINI) or a current MDD (as assessed by the patient-rated PHQ-9).

The required sample size was based on a desired level of precision, with a larger sample providing a more precise estimate of the population parameter of interest. A sample of 400 patients would provide a 95% CI (precision) width of 9.8% if the proportion of MDE in this sample was as high as 50%. A CI width of <10% was considered sufficient precision for the estimation of the primary endpoint.

In an attempt to recruit a "real-world" sample of patients, few inclusion and exclusion criteria were specified. All eligible participants were invited to participate, and the reasons for nonparticipation were recorded. All patients who provided consent to release information and who fulfilled the patient eligibility criteria were included in the analyses.

All analyses were specified before data collection in the study protocol and subsequently conducted without deviation. Descriptive summary statistics included the number and percentage for categorical variables and the number, mean, median, standard deviation (SD), minimum, and maximum for continuous variables. Unless otherwise specified, differences between

the group of patients who met the criteria for a current MDE (MDE+ group) and the group of patients who did not meet the criteria (MDE- group) were assessed using a t test and 95% CIs.

The association between (i) pain and (ii) quality of life and the predictor variables, depression and anxiety, was investigated using analysis of covariance (ANCOVA). The ANCOVA models were adjusted for the following pre-specified covariates: age, sex, investigator, anxiety severity (HADS anxiety subscale total score), depression severity (PHQ-9 total score), treatment taken for pain in the past 3 months (no treatment vs drug treatment, non-drug treatment vs drug treatment), treatment taken for depression in the past 3 months (no treatment vs drug treatment, non-drug treatment vs drug treatment), and the number of comorbidities. The association between quality of life and depression and anxiety was also adjusted for pain severity (pain VAS score).

Statistical analyses were conducting using SAS® software (version 9.01.01, SAS Institute, Cary, N.C.) and R programming language.[29]

## RESULTS

*Patient disposition*

A total of 817 patients who met the eligibility criteria were asked to participate in the study, of whom 402 patients (49.2%) agreed to participate and were enrolled in the study. The three most common reasons for not participating in the study, in the investigator's opinion, were 'Having no interest in clinical research', 'Unwilling to provide data', and 'Believing participation in the study would not benefit their treatment'.

*Primary objective*

All of the enrolled patients completed the study questionnaires. Of the 402 patients enrolled in the study, 197 patients (49.0%; 95% CI: 44.0 to 54.0) met the criteria for a current MDE (MDE+ group) and 205 patients (51.0%) did not meet the criteria (MDE- group).

*Patient characteristics*

In general, the characteristics of the MDE+ and MDE- groups were similar (Table 1). The median duration of pain at the most recent site of persistent pain was longer in the MDE- group than the MDE+ group (15.0 vs 11.3 months, p=0.016, Wilcoxon). However, the distribution of the duration of pain at the most recent site of persistent pain was highly skewed in both groups (maximum of 199.1 and 239.1 months in the MDE+ and MDE- groups, respectively) and the two distributions were similar in appearance.

*Pain and somatic symptoms*

The mean (SD) pain severity VAS score of the study population was 60.3 (24.26) mm (Figure 1A) and the mean SSI-28 pain item score (SD) was 2.3 (0.83) (Figure 1B). In the entire study population, the most common pain-related somatic symptoms that patients reported being bothered by moderately, quite a bit, or a great deal during the past week were 'headaches' (207/402, 51.5%), 'soreness in your muscles' (178/402, 44.3%), and 'neck pain' (171/402, 42.5%). In addition, the most common non-pain-related somatic symptoms that patients reported being bothered by moderately, quite a bit, or a great deal were 'feeling that you are not in as good physical health as most of your friends' (221/402, 55.0%) and 'feeling fatigued, weak or tired all over' (213/402, 53.0%).

The mean pain severity score was significantly higher in the MDE+ group than the MDE- group (between-group difference: 9.6 mm, 95% CI: 5.0 to 14.3, p<0.001; Figure 1A). Similarly, the mean SSI-28 pain item score was 0.5 units higher in the MDE+ group than the MDE- group (95% CI: 0.3 to 0.7, p<0.001; Figure 1B), indicating that the MDE+ group, on average, had been bothered by pain-related symptoms to a greater extent during the past week than patients in the MDE- group. A higher proportion of patients in the MDE+ group than in the MDE- group reported being bothered moderately, quite a bit, or a great deal by each of the seven pain-related somatic symptoms (Table 2). In particular, higher proportions of patients in the MDE+ group than in the MDE- group were more bothered by 'pains or cramps in your abdomen' and 'pains in your head or chest'.

The mean SSI-28 non-pain item score was 0.6 units higher in the MDE+ group than the MDE- group (95% CI: 0.5 to 0.7, p<0.001; Figure 1C), indicating that the MDE+ group, on average, had been bothered by non-pain-related symptoms to a greater extent during the past week than the MDE- group. A higher proportion of patients in the MDE+ group than in the MDE- group reported being bothered moderately, quite a bit, or a great deal by each of 21 non-pain-related somatic symptoms (data not shown). In particular, higher proportions of patients in the MDE+ group

**Table 1: Patient characteristics**

| Characteristic | All patients (N = 402) | MDE+ (N = 197) | MDE- (N = 205) |
|---|---|---|---|
| Median age, years | 43.0 | 42.0 | 44.0 |
| Minimum, maximum | 18, 66 | 18, 65 | 19, 66 |
| Female, n (%) | 279 (69.4) | 137 (69.5) | 142 (69.3) |
| Marital status, n (%) | | | |
| Married, living together | 328 (81.6) | 152 (77.2) | 176 (85.9) |
| Divorced | 3 (0.7) | 1 (0.5) | 2 (1.0) |
| Widowed | 7 (1.7) | 3 (1.5) | 4 (2.0) |
| Partnered, living together | 6 (1.5) | 2 (1.0) | 4 (2.0) |
| Married, living separate | 14 (3.5) | 12 (6.1) | 2 (1.0) |
| Partnered, living separate | 2 (0.5) | 0 (0) | 2 (1.0) |
| No relationship | 42 (10.4) | 27 (13.7) | 15 (7.3) |
| Work status[a], n (%) | | | |
| Full-time | 209 (52.0) | 91 (46.2) | 118 (57.6) |
| Part-time | 29 (7.2) | 20 (10.2) | 9 (4.4) |
| Retired | 81 (20.1) | 34 (17.3) | 47 (22.9) |
| Student | 25 (6.2) | 17 (8.6) | 8 (3.9) |
| Unemployed | 42 (10.4) | 25 (12.7) | 17 (8.3) |
| Unemployed because of study condition | 16 (4.0) | 10 (5.1) | 6 (2.9) |
| Living arrangements[a], n (%) | | | |
| Independent (living in own apartment or house) | 63 (15.7) | 31 (15.7) | 32 (15.6) |
| Family | 331 (82.3) | 159 (80.7) | 172 (83.9) |
| Non-relative | 8 (2.0) | 7 (3.6) | 1 (0.5) |
| Education, n (%) | | | |
| No formal education | 30 (7.5) | 13 (6.6) | 17 (8.3) |
| Primary education | 176 (43.8) | 90 (45.7) | 86 (42.0) |
| Secondary education | 139 (34.6) | 66 (33.5) | 73 (35.6) |
| Tertiary education | 57 (14.2) | 28 (14.2) | 29 (14.1) |
| Number of co-morbidities, n (%) | | | |
| 0 | 265 (65.9) | 131 (66.5) | 134 (65.4) |
| 1 | 94 (23.4) | 49 (24.9) | 45 (22.0) |
| 2 | 36 (9.0) | 16 (8.1) | 20 (9.8) |
| ≥3 | 7 (1.7) | 1 (0.5) | 6 (2.9) |
| Duration of pain in the most recent site of persistent pain, months | | | |
| Median | 12.4 | 11.3 | 15.0 |
| Minimum, maximum | 3.0, 239.1 | 3.0, 199.1 | 3.1, 239.1 |

[a] For the majority of the time during the past 6 months.
Abbreviations: MDE+ = met the MINI criteria for a current major depressive episode; MDE- = did not meet the MINI criteria for a current major depressive episode; MINI = Mini-International Neuropsychiatric Interview.

than in the MDE- group were more bothered by 'feeling faint or dizzy', 'feeling fatigued, weak or tired all over', 'indigestion, upset stomach or acid stomach', 'feeling weak in parts of your body', and 'heavy feelings in your arms and legs'.

*Depression*

There was clinically significant depression in the study population. The mean (SD) PHQ-9 total score of the study population was 10.5 (6.93) (Figure 1D). Approximately half of the study

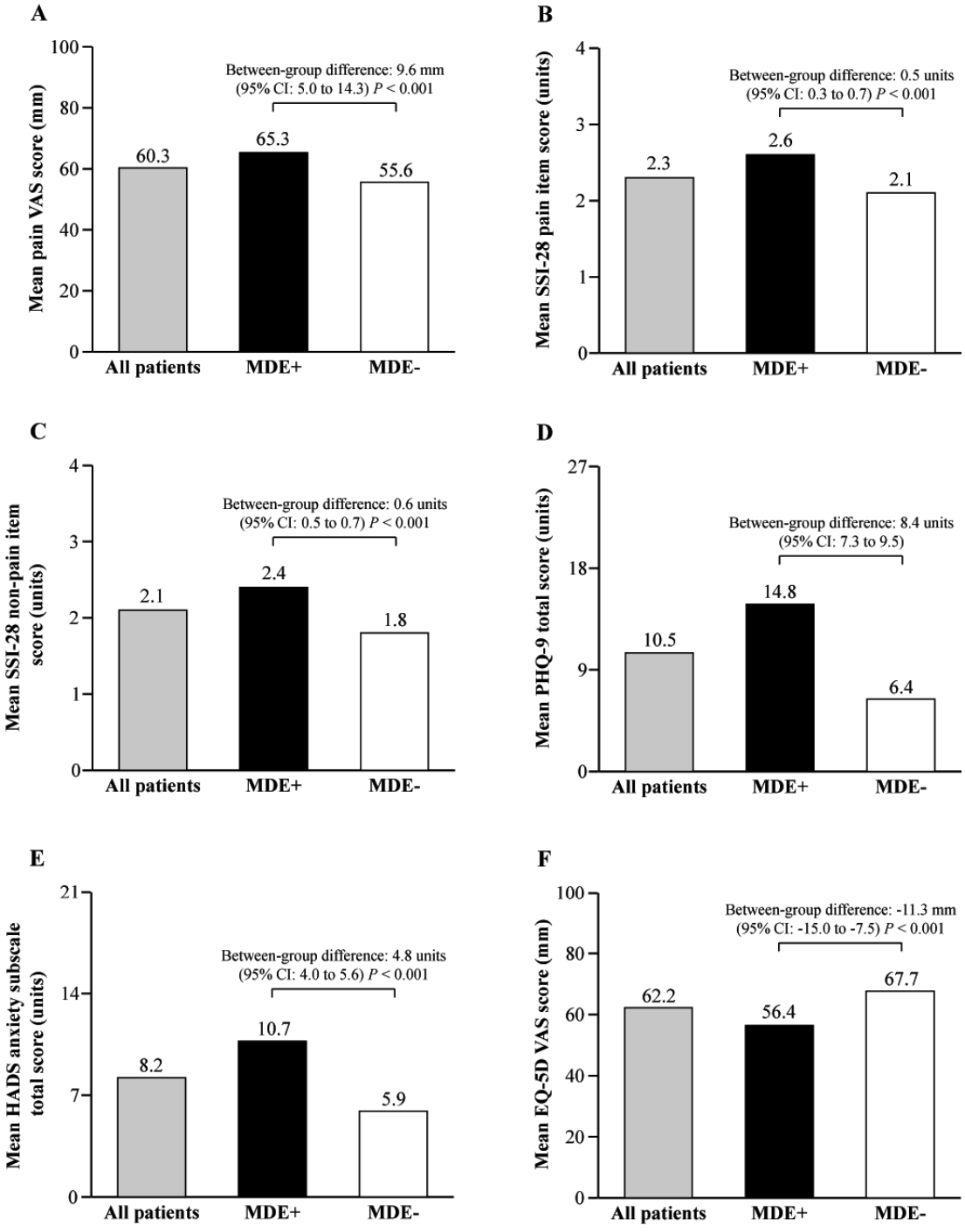


Figure 1: Assessment of pain (A), pain-related somatic symptoms (B), non-pain-related somatic symptoms (C), depression (D), anxiety (E), and health-related quality of life (F) in the entire study population and the MDE+ and MDE- groups. For each of the scales/questionnaires except the EQ-5D VAS, the higher the score, the more severe the condition under assessment.

Abbreviations: EQ-5D = EuroQoL-5 Dimensions; HADS = Hospital Anxiety and Depression Scale; MDE+ = met the MINI criteria for a current major depressive episode; MDE- = did not meet the MINI criteria for a current major depressive episode; MINI = Mini-International Neuropsychiatric Interview; PHQ-9 = 9-item Patient Health Questionnaire; SSI-28 = modified 28-item Somatic Symptom Inventory; VAS = visual analogue scale.

**Table 2: The proportions of patients who were bothered by the pain-related somatic symptoms in the SSI-28 questionnaire moderately, quite a bit, or a great deal during the week before the study visit**

| Pain-related symptom | All patients (N = 402) n (%) | MDE+ (N = 197) n (%) | MDE- (N = 205) n (%) |
|---|---|---|---|
| Soreness in your muscles | 178 (44.3) | 101 (51.3) | 77 (37.6) |
| Pains or cramps in your abdomen | 83 (20.6) | 55 (27.9) | 28 (13.7) |
| Pains in your lower back | 152 (37.8) | 87 (44.2) | 65 (31.7) |
| Pains in your head or chest | 93 (23.1) | 61 (31.0) | 32 (15.6) |
| Headaches | 207 (51.5) | 115 (58.4) | 92 (44.9) |
| Pains in your joints | 131 (32.6) | 79 (40.1) | 52 (25.4) |
| Neck pain | 171 (42.5) | 101 (51.3) | 70 (34.1) |

Abbreviations: MDE+ = met the MINI criteria for a current major depressive episode; MDE- = did not meet the MINI criteria for a current major depressive episode; MINI = Mini-International Neuropsychiatric Interview; SSI-28 = modified 28-item Somatic Symptom Inventory.

population (206/402, 51.2%) rated their severity of depression as moderate, moderately severe, or severe (Table 3).

As expected, the severity of depression was higher in patients who met the criteria for a current MDE compared with those who did not meet the criteria. The mean PHQ-9 total score was 8.4 units (95% CI: 7.3 to 9.5; $p<0.001$) higher in the MDE+ group than the MDE- group (Figure 1D). A higher percentage of patients in the MDE+ group than the MDE- group had PHQ-9 total scores indicative of moderately severe or severe depression (99/197, 50.3% vs 16/205, 7.8%; Table 3).

There was a relatively high level of agreement between the proportion of patients who met the criteria for a current MDE as assessed by the clinician-rated MINI and the proportion of patients who met the criteria for MDD as assessed by the patient-rated PHQ-9. Of the 197 patients who met the MINI criteria for a current MDE (MDE+), 102 patients (51.8%) also met the criteria for suspected MDD based on their PHQ-9 total score. Of the 205 patients who did not meet the MINI criteria for a current MDE (MDE-), 188 patients (91.7%) also did not meet the criteria for suspected MDD based on their PHQ-9 total score.

**Table 3: Depression severity categories based on the patients' PHQ-9 total scores**

| Depression severity category | PHQ-9 total score | All patients (N = 402) n (%) | MDE+ (N = 197) n (%) | MDE- (N = 205) n (%) |
|---|---|---|---|---|
| None | 0-4 | 94 (23.4) | 10 (5.1) | 84 (41.0) |
| Mild | 5-9 | 102 (25.4) | 28 (14.2) | 74 (36.1) |
| Moderate | 10-14 | 91 (22.6) | 60 (30.5) | 31 (15.1) |
| Moderately severe | 15-19 | 61 (15.2) | 47 (23.9) | 14 (6.8) |
| Severe | 20-27 | 54 (13.4) | 52 (26.4) | 2 (1.0) |

Abbreviations: MDE+ = met the MINI criteria for a current major depressive episode; MDE- = did not meet the MINI criteria for a current major depressive episode; MINI = Mini-International Neuropsychiatric Interview; PHQ-9 = 9-item Patient Health Questionnaire.

*Anxiety*

Anxiety was generally not severe in the study population. The mean (SD) HADS anxiety subscale total score of the entire study population was 8.2 (4.76) (Figure 1E). The mean anxiety subscale score was significantly higher in the MDE+ group than the MDE- group (between-group difference: 4.8 units, 95% CI: 4.0 to 5.6, p<0.001; Figure 1E).

*Health-related quality of life*

There was some impairment in health-related quality of life in the study population. The mean (SD) EQ-5D VAS score of the entire study population was 62.2 mm (19.80) (Figure 1F). The mean EQ-5D VAS score was significantly lower in the MDE+ group than the MDE- group. The between-group difference in the mean EQ-5D VAS score was -11.3 mm (95% CI: -15.0 to -7.5, p<0.001; Figure 1F).

*Association between pain and depression*

The ANCOVA model indicated that each increase of 1.0 unit in the PHQ-9 total score was associated with a 0.97 mm increase in the pain VAS score (95% CI: 0.50 to 1.43). However, the model fit was poor ($R^2 = 0.2116$), indicating that the interrelationships were complex and not well described by a linear statistical model. An exploratory scatterplot confirmed a weak positive relationship between PHQ-9 total score and pain VAS score (data not shown).

The ANCOVA model indicated that each increase of 1.0 mm in the pain VAS score was associated with a 0.16 mm decrease in the EQ-5D VAS score (95% CI: -0.24 to -0.08); each increase of 1.0 unit in the PHQ-9 total score was associated with a 1.01 mm decrease in the EQ-5D VAS score (95% CI: -1.37 to -0.64). However, the model fit was poor ($R^2 = 0.3286$), indicating that the complex interrelationships between these and other factors were not well described by a linear statistical model.

*Treatment for pain, depression, and/or anxiety*

The majority of patients had not taken any drug or non-drug treatments for pain (275/402, 69.1%), depression (344/402, 85.8%), or anxiety (353/402, 88.0%) in the past 3 months. Only 14.2% of patients in the study population, and 16.3% of patients in the MDE+ group, had received any treatment for depression in the past 3 months (Table 4). At the study visit, when treatment could be initiated or changed, there was an increase in the number of patients in the entire study population who were prescribed treatment for pain (164/402, 40.8%), depression (234/402, 58.2%), or anxiety (183/402, 45.5%).

Similar proportions of patients in the MDE+ and MDE- groups (16.3% and 12.2%, respectively) had received treatment for depression in the past 3 months; at the study visit, 75.6% of patients in the MDE+ group were prescribed treatment for depression compared with 41.5% of patients in the MDE- group. Higher proportions of patients in the MDE+ group were also prescribed treatment for pain and anxiety at the study visit compared with the MDE- group (Table 4). Relatively few patients in both groups were prescribed non-drug treatments for pain, depression, or anxiety.

## DISCUSSION

To our knowledge, this is the first study conducted in China to examine the frequency of major depression in a large sample of patients with chronic, medically unexplained PPS. Almost half of the patients in the study met the criteria for a current MDE, and approximately 80% of these patients had PHQ-9 scores indicative of moderate or severe depression. Despite the apparently high frequency of MDE in the study population, only a small proportion of patients had received any treatment for depression during the past 3 months. These results indicate that symptoms of depression were common and were generally not being treated in this group of Chinese patients who presented to neurology clinics with medically unexplained PPS as the presenting complaint.

The frequency of MDE observed in this study was higher than the prevalence of depression observed in three small observational studies conducted in neurology (43 patients)[30], pain (120 patients)[31], and rehabilitation (198 patients)[32] clinics in China. These studies found that approximately 30% of patients with chronic (≥6 months), medically unexplained PPS had depressive symptoms. However, in these studies depression was assessed using the Self-rating Depression Scale (SDS) rather than the Diagnostic and Statistical Manual of Mental Disorders (4th edition; DSM-IV) criteria or module A of the MINI and, therefore, may have been under-reported. The frequency of MDE in our study was similar to, or greater than, that observed in three previous studies conducted in neurology clinics in the United States and Europe.[21-23] In a study conducted in neurology clinics in

**Table 4: Proportion of patients receiving treatment for pain, depression, and/or anxiety**

| Characteristic | All patients (N = 402) n (%) | MDE+ (N = 197) n (%) | MDE- (N = 205) n (%) |
|---|---|---|---|
| Treatment taken for pain in the past 3 months | | | |
| Number of respondents | 398 | 196 | 202 |
| Received treatment | 123 (30.9) | 62 (31.6) | 61 (30.2) |
| Non-drug | 34 (8.5) | 15 (7.7) | 19 (9.4) |
| Drug | 89 (22.4) | 47 (24.0) | 42 (20.8) |
| Treatment taken for depression in the past 3 months | | | |
| Number of respondents | 401 | 196 | 205 |
| Received treatment | 57 (14.2) | 32 (16.3) | 25 (12.2) |
| Non-drug | 1 (0.2) | 1 (0.5) | 0 (0) |
| Drug | 56 (14.0) | 31 (15.8) | 25 (12.2) |
| Treatment taken for anxiety in the past 3 months | | | |
| Number of respondents | 401 | 196 | 205 |
| Received treatment | 48 (12.0) | 28 (14.3) | 20 (9.8) |
| Non-drug | 3 (0.7) | 2 (1.0) | 1 (0.5) |
| Drug | 45 (11.2) | 26 (13.3) | 19 (9.3) |
| Treatment prescribed for pain at the visit | | | |
| Number of respondents | 402 | 197 | 205 |
| Prescribed treatment | 164 (40.8) | 97 (49.2) | 67 (32.7) |
| Non-drug | 14 (3.5) | 8 (4.1) | 6 (2.9) |
| Drug | 150 (37.3) | 89 (45.2) | 61 (29.8) |
| Treatment prescribed for depression at the visit | | | |
| Number of respondents | 402 | 197 | 205 |
| Prescribed treatment | 234 (58.2) | 149 (75.6) | 85 (41.5) |
| Non-drug | 2 (0.5) | 2 (1.0) | 0 (0) |
| Drug | 232 (57.7) | 147 (74.6) | 85 (41.5) |
| Treatment prescribed for anxiety at the visit | | | |
| Number of respondents | 402 | 197 | 205 |
| Prescribed treatment | 183 (45.5) | 121 (61.4) | 62 (30.2) |
| Non-drug | 1 (0.2) | 1 (0.5) | 0 (0) |
| Drug | 182 (45.3) | 120 (60.9) | 62 (30.2) |

Abbreviations: MDE+ = met the MINI criteria for a current major depressive episode; MDE- = did not meet the MINI criteria for a current major depressive episode; MINI = Mini-International Neuropsychiatric Interview.

the United States, approximately one-third of newly referred patients received no neurological diagnosis for their symptoms; of these patients, 43% were found to have an underlying psychiatric disorder.[23] In another study conducted the United States, in which 33% of patients with pain also had depression, neurologists were more likely to recognize and treat pain than depression.[22] In contrast, in a study conducted in neurology clinics in Europe, where 47% of newly referred patients met the criteria for one or more DSM-IV anxiety or depressive diagnosis, neurologists were likely to suggest psychiatric/psychological treatment for patients with an emotional disorder and unexplained symptoms, but few patients expressed enthusiasm for such treatment.[21] The prevalence of depression in patients with pain presenting to neurology clinics in these studies, and in the current study, was generally higher than that observed in patients with pain presenting to primary care clinics[2,22], which in the systematic review published by Bair et al. (2003) was reported to range from 5.9% to 46% (mean 27%).[2] Taken together, these results underline the need for

neurologists to be aware of the possibility of depression in patients presenting with PPS.

Compared with the MDE- group, patients in the MDE+ group tended to have more severe pain and anxiety, and a worse perceived health state, indicating that depression often presents with painful and anxiety symptoms, and that depression adds a significant psychological and emotional burden to patients with PPS. Concomitant depression can increase the morbidity of pain and complicate pain treatment.[2,7,10,13] Therefore, it is important that depression in patients with PPS is recognized and treated. An observational study on PPS in Chinese patients with MDD showed that patients with PPS reported greater severity of pain and depression, poorer quality of life, and a less satisfactory treatment response compared with those without PPS.[20] Taken together, these results suggest that Chinese patients with both chronic painful symptoms and depression may have a greater burden of disease and a poorer quality of life compared with patients with either condition alone.

In our study, the ANCOVA model that was used to assess the association between pain and depression showed that increased pain severity was associated with increased depression severity. However, the model fit was poor and, therefore, it is difficult to draw strong conclusions from this model. In addition, while it is possible to conclude there was a positive relationship between pain and depression in this study, it is not possible to deduce causality because of the cross-sectional study design. The relationship between pain and depression is complex. Numerous studies indicate that: (i) depression is associated with an increased risk of chronic pain and vice versa; (ii) the presence of one condition hinders treatment of the other; and (iii) pain severity increases when the severity of depressive symptoms increase.[2,3,6-8,10-13,15-20,33] At a biological level, alterations in the serotonergic and noradrenergic systems of the central nervous system have been implicated in the pathophysiology of both chronic pain and depression, and in the association between pain and depression. However, the relationship between pain and depression is still not fully understood.[34]

While a lack of treatment may not necessarily equate to a lack of diagnosis, the relatively low proportion of patients (14.2%) who received treatment for depression during the 3 months before the study visit suggests that depression was underdiagnosed in this patient population. This underdiagnosis of depression may be related to patients and their physicians attributing the PPS to an underlying medical illness rather than considering the possibility of an underlying depressive disorder.[2,3] Possible reasons for this could be that patients with depression may present with physical symptoms rather than depressive symptoms or patients may be reluctant to report depressive symptoms because of a perceived stigma of depression and choose to report the physical symptoms only. Cultural factors may influence the pattern of symptoms reported by patients with depression. Previous research has indicated that patients in non-Western or developing countries are more likely to report physical symptoms rather than emotional symptoms compared with patients in developed, Western countries.[35-37] Some studies have suggested that Chinese people may deny depression or express it somatically.[38,39] However, there is also evidence to indicate that although Chinese patients may initially volunteer physical symptoms only, more specific, structured questioning yields appropriate information on depressive symptoms.[39,40] A similar finding was observed in this study. In addition, it has been suggested that one of the factors contributing to the recent increases observed in the reported prevalence of depression in China is that Chinese people are becoming more willing to express emotional symptoms. This appears to be a result of the rapid socioeconomic changes in China over the past two decades and mental health becoming an understandable and acceptable concept.[41,42] Regardless of the reason for patients presenting with PPS only, focusing on the physical symptoms may result in unnecessary tests, delayed or underdiagnosis of depression, and incorrect treatment, all of which can lead to increased use of medical resources and higher health care costs.[34]

Although all of the patients in the study had PPS, the majority of patients (69%) had not taken any treatment for pain in the past 3 months. This reflects the real-world situation for many patients in clinical practice in China, who may tolerate painful symptoms for a long time before seeking treatment, and often prefer to receive treatment in the following order: no treatment; non-drug treatment; traditional remedies; drug treatment. In addition, safety and affordability may be major considerations when making treatment decisions.

The clinician-rated MINI and the patient-rated PHQ-9 were highly concordant for the absence of MDE and MDD, but there was less agreement between the two questionnaires for the presence of

MDE and MDD. However, the two scales were not designed to be used in the same way. The MINI interview is conducted by physicians for diagnostic purposes and the PHQ-9 is a patient-rated questionnaire used to assess the severity of depression as a screening tool for depression. Therefore, complete agreement between the two scales would not be expected. The less-than-high degree of concordance suggests that the PHQ-9, which is simple and easy to administer, could be used as a screening tool to assess whether the patient may have symptoms of major depression and should be referred to an appropriate physician for further assessment and treatment. However, further work is necessary to assess whether a lower cut-off in these Chinese patients would be advisable.

This study used a simple, naturalistic study design in the "real-world" setting of general neurology clinics, which is the most common clinical setting in China where patients with chronic, medically unexplained PPS receive treatment. While this study provides current data for major hospitals in urban areas of China, the information may not be representative of all regions of China. In addition, although efforts were made to ensure that a representative sample was enrolled, by recruiting patients from a number of sites with minimal eligibility criteria, the study population cannot be taken as a purely random sample. Of the patients screened for the study, 51% met the enrolment criteria but did not agree to participate and, therefore, the possibility of selection bias and nonresponse bias needs to be considered when generalizing these results to a wider population. Another limitation of the study is that the substantial increase in the proportion of patients receiving treatment for pain, depression, and/or anxiety at the study visit compared with the previous 3 months may have been a direct consequence of participating in the study, although the investigators were asked to follow their usual clinical practice while participating in the study. Another possibility for the increase in prescribed treatments is that the investigators were seeing these patients for the first time and considered it necessary to adjust their medication. The nature of the relationship between patients and physicians in tertiary care may also have led patients to agree to treatment. Furthermore, it may have been a relatively long time since some of the patients had seen a physician, and many may have tried traditional or non-drug therapies in the past. Other limitations of the study include the lack of information collected about the patients' use of treatments more than 3 months before the study visit or whether any of the patients had previously been diagnosed with depression, and the lack of assessment of the total duration of PPS, which may influence the severity of depression.

In conclusion, almost half of the patients in this large sample of patients presenting with chronic, medically unexplained PPS at general neurology clinics in China met the criteria for a current MDE, and the majority of these patients rated the severity of their depression as moderate or worse. The overall severity of pain and anxiety was higher, and the mean perceived health state was lower, in the patients who met the criteria for a current MDE compared with those patients who did not meet the criteria. Despite the relatively high proportion of patients with depressive symptoms, only a minority of patients had been receiving treatment for depression at the time of the study. These results add to the available evidence indicating that an increased awareness of the potential for major depression is needed, and that both physical and depressive symptoms need to be recognized and addressed. While not all PPS indicate depression, awareness of this possibility would contribute to the overall treatment strategy for the patient, and could potentially lead to improved outcomes in patients with chronic, medically unexplained PPS.

## DISCLOSURE

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*Role of the sponsor:* Eli Lilly was involved in the study design, data collection, data analysis, and preparation of the manuscript.

*Authors' contributions:* All authors participated in the interpretation of the study results, and in the drafting, critical revision, and approval of the final version of the manuscript. In addition,

JR, SH, and SW were involved in study design, data collection, and statistical analysis. RW was involved in statistical analysis and JJ contributed to the design of the study. JJ, WQ, WW, LW, LM, DZ, and ZH were clinical investigators in the trial and were involved in data collection.

*Conflicts of interest:* JR, SH, RW, and SW are full-time employees of Eli Lilly and Company. JR and RW own stock in Eli Lilly and Company. JJ, WQ, WW, LW, LM, DZ, and ZH have no conflicts of interest to disclose.

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