Sex Differences in the Prevalence and Clinical Features of Comorbid Depressive Symptoms in Never-Treated Chinese Patients With First-Episode Schizophrenia

Dong-Mei Wang, PhD[a]; Guang-Ya Zhang, MD[b]; Xiang-Dong Du, MD[b]; Qiu-Fang Jia, MD[b]; Zheng-Kang Qian, MD[b]; Guang-Zhong Yin, MD[b]; Da-Chun Chen, MD[c]; Mei-Hong Xiu, PhD[c]; Yu-Ping Ning, MD, PhD[d,e]; Xing-Bing Huang, MD[d]; Feng-Chun Wu, MD, PhD[d,e]; and Xiang-Yang Zhang, MD, PhD[a,d,*]

ABSTRACT

Background: Many studies have indicated a sex-specific effect in many aspects of schizophrenia. The presence of depressive symptomatology exists in all phases of schizophrenia. The aim of this study is to investigate the sex differences in the proportion of comorbid depressive symptoms and sex-specific relationships between depressive symptoms and clinical correlates in never-treated Chinese patients with first-episode schizophrenia (NTFE patients), which have not been reported yet.

Methods: Via a cross-sectional design, 240 NTFE inpatients (male/female = 111/129) between ages 16 and 45 years and meeting *DSM-IV-TR* criteria of schizophrenia were recruited. The Positive and Negative Syndrome Scale (PANSS) was used for the psychopathology, and the 17-item Hamilton Depression Rating Scale (HDRS-17) for the comorbid depressive symptoms. This study was conducted from June 2013 to December 2015.

Results: The proportion of patients with depressive symptoms (total score on HDRS-17 ≥ 8) in men was significantly higher than in women (male: 62.2%, female: 48.1%; $\chi^2_1 = 4.28$, $P = .039$). Male patients had significantly greater depressive symptoms as shown on the HDRS-17 than female patients ($t_{1,238} = 2.75$, $P = .006$). Further, we found that age, the age at onset, smoking rate, and PANSS total and general psychopathology, negative symptoms, and cognitive factor subscores favored significant sex differences in female patients (all $P < .05$). Interestingly, we found sex differences in the correlation between the HDRS-17 score and clinical phenotype, showing that in male patients, the PANSS general psychopathology subscore ($\beta = 0.75$, $t = 7.72$, $P < .001$) and total score ($\beta = 0.44$, $t = 4.81$, $P < .001$) significantly predicted the HDRS-17 total score, while in female patients, the PANSS general psychopathology subscore ($\beta = 0.74$, $t = 8.45$, $P < .001$), total score ($\beta = 0.47$, $t = 5.71$, $P < .001$), and cognitive factor subscore ($\beta = 0.24$, $t = 2.60$, $P < .001$) significantly predicted the HDRS-17 total score.

Conclusions: Our results indicate sex differences in the frequency and severity of comorbid depressive symptoms and in associations between depressive symptoms and clinical correlates in NTFE patients.

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[a]CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China
[b]Suzhou Psychiatric Hospital, The Affiliated Guangji Hospital of Soochow University, Suzhou, Jiangsu Province, China
[c]Beijing Huilongguan Hospital, Beijing, China
[d]The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China
[e]Guangdong Engineering Technology Research Center for Translational Medicine of Mental Disorders, Guangzhou, China
*Corresponding author: Xiang-Yang Zhang, MD, PhD, 16 Lincui Rd, Chaoyang District, Beijing 100101, China (zhangxy@psych.ac.cn).

Many studies have shown that sex differences exist in many aspects of schizophrenia. For instance, the age at onset is earlier in male schizophrenia patients.[1–3] Also, sex differences have been present in symptomatology, cognitive performance, treatment response, and long-term outcome.[4–10] Some studies[1,11–15] have indicated that female patients have more severe symptoms, especially negative symptoms, and perform worse in cognitive tests than male patients. Moreover, female patients have been shown to have better responses and fewer side effects than male patients during the course of antipsychotic treatment.[3,10,16,17] In addition, women with schizophrenia appear to have better global outcomes and function better socially than men with schizophrenia.[11,18] Although the findings of sex differences in schizophrenia are often inconsistent, most studies have demonstrated that women with schizophrenia may have more favorable clinical presentations and a better psychosocial outcome than men with schizophrenia,[1,7,19] probably due to the neuroprotective effects of the female sex hormones.[20–22]

Comorbid depressive symptoms are frequently seen in schizophrenia, with the rate of depressive symptoms varying greatly, ranging from 6% to 65%.[9,23–25] These inconsistent results may be due to the different definitions, observational intervals, treatment situations, and instruments utilized to measure depressive symptoms.[25,26] A few long-term studies[9,26–28] have shown that 25%–40% of patients with schizophrenia are still presenting at least 1 depressive symptom after remission of psychosis and remain stable thereafter, indicating a persistent group of comorbid depressed patients with schizophrenia.[28] The comorbid depression in schizophrenia patients has been related to other symptoms, especially negative symptoms, likelihood of hospitalization, and suicide risk,[29–31] while negatively related to clinical outcome,[28] quality of life, and social functioning.[32] However, investigations regarding depressive symptoms in schizophrenia have remained limited.

Clinical Points

- We examined sex differences in the prevalence rate and clinical characteristics of comorbid depressive symptoms in never-treated patients with first-episode schizophrenia.
- We found higher incidence rates of co-occurring depression, together with significantly greater depressive symptoms and clinical symptoms, in male than in female patients.
- Further, we found sex differences in the correlations of co-occurring depressive symptoms with clinical parameters.

Sex differences in mood disorder are eminent, and many studies[33–35] have reported that depression rates in women are about twice those of men in both adults and adolescents. Moreover, sex differences were present in the severity of depressive symptoms and responses to antidepressants.[36] Some recent studies have shown sex differences in depressive symptoms among chronic ketamine users[37] and patients with overactive bladder.[38] In spite of the close relationship of comorbid depressive symptoms with schizophrenia, whether sex differences in depressive symptoms may also occur in schizophrenia has not been reported yet.

Further, although many studies have reported that comorbid depression is common among patients with schizophrenia as mentioned above, few studies[9,39] have examined the correlation of co-occurring depressive symptoms with schizophrenia in never-treated patients with first-episode schizophrenia (NTFE patients). It is well established that studying NTFE patients has a prominent advantage in minimizing some main confounders such as duration of illness, the effect of medication treatment, medical comorbidities, and medication side effects that are correlated with symptoms of chronic schizophrenia.[40] Therefore, the main focus of this study was to evaluate sex differences in the prevalence rate and clinical characteristics of comorbid depressive symptoms in NTFE patients in a Chinese Han population, which to our knowledge, has not been investigated. Our hypothesis is that (1) the incidence of co-occurring depressive symptoms in NTFE patients would be higher in women than in men and (2) there would be sex differences in depressive symptoms and psychotic symptoms, and further in their relationships in NTFE patients.

METHODS

Subjects

We recruited 240 NTFE patients (111 men and 129 women) from Beijing HuiLongGuan Hospital, a public psychiatric hospital in the Beijing area and one of the largest psychiatric hospitals in China, with about 400 outpatient visits per day and more than 1,400 inpatient beds specializing in the treatment of all kinds of psychiatric patients. Thus, the clinical setting in this study was representative of the acute inpatient care for schizophrenia in China. The study was conducted from June 2013 to December 2015. Two experienced psychiatrists used the Chinese version of the Structured Clinical Interview for *DSM-IV-TR* (SCID-I)[41] to diagnose each patient at baseline and at 3–6 months follow-up. The subjects met the following criteria: Chinese Han patients (1) between ages 16 and 45 years, (2) with acute episode at admission, (3) duration of symptoms ≤ 60 months, and (4) not having received any antipsychotic treatment.

Patients were physically examined and complete medical history information was obtained. The exclusion criteria included (1) current major physical disease, (2) personal or family history of neurologic diseases, (3) history of alcohol or substance dependence other than smoking, or (4) inability to provide signed consent.

Of the 268 eligible subjects, 28 (10.4%) were excluded due to the following reasons: 7 did not satisfy the inclusion criteria, 8 refused to sign the informed consent form, and 13 were unable to comprehend consent procedures or had an acute clinical status that made interviewing difficult or unreliable. The study protocol was approved by the Research Ethics Review Board of Beijing HuiLongGuan Hospital. All subjects signed a written informed consent form after the study had been adequately explained.

Clinical Measures

Research staff was in charge of collecting general and demographic data, cigarette smoking status, and medical and psychological status through detailed questionnaires. More information was obtained from personal medical records, the patients' families, and therapy clinicians.

The Positive and Negative Syndrome Scale[42] (PANSS) was used to evaluate the psychopathology, and the 17-item Hamilton Depression Rating Scale[43] (HDRS-17) was used to assess the comorbid emotional symptoms. To maintain assessment consistency of the scales, 4 psychiatrists, who had at least 5 years of experience in clinical practice, were responsible for administering the scales. The interrater correlation coefficient for repeated assessment for the PANSS and HDRS-17 total scores was greater than 0.8. The "cognitive factor" subscore was extracted from the 5-factor model of the PANSS scores.[44]

We used the HDRS-17 to measure comorbid depressive symptoms. A cutoff value was used to classify the 2 groups. Patients with depression were defined as having a total HDRS-17 score ≥ 8, while patients with "nondepression" were defined as having a total score ≤ 7.[43]

Statistical Analysis

Demographic and clinical characteristics were compared between male and female patients using χ^2 tests for categorical variables and Student *t* tests for continuous variables. Pearson χ^2 test was used to determine the incidence rate of co-occurring depression symptoms in male and female patients, respectively. Odds ratios (ORs) were calculated with logistic regression between depressed and nondepressed groups after correcting the relevant variables. To compare the sex differences in depressive symptoms and clinical parameters, analysis of covariance

Table 1. Characteristics of Male and Female Patients With NTFE Schizophrenia

Characteristic	Male Patients (n = 111)[a]	Female Patients (n = 129)[a]	*t* or χ^2	*P* Value
Age, y	26.4 ± 8.4	29.8 ± 10.0	−2.86	.005
Education, y	12.3 ± 3.7	12.5 ± 3.5	−0.50	.62
Body mass index, y	22.1 ± 3.7	21.9 ± 3.9	0.33	.74
Smoker, n (%)	57 (51)	8 (6)	61.6	< .001
Age at onset, y	24.4 ± 8.2	27.7 ± 9.9	−2.77	.006
PANSS				
Positive symptom subscale	25.7 ± 7.3	25.6 ± 5.9	0.14	.89
Negative symptom subscale	21.4 ± 8.8	18.5 ± 6.8	2.81	.005
General psychopathology subscale	43.7 ± 12.7	38.9 ± 8.8	3.44	.001
Total score	90.8 ± 21.4	83.0 ± 16.1	3.21	.002
Cognitive factor	8.8 ± 4.2	7.2 ± 3.2	3.23	.001
HDRS-17 total score	11.2 ± 8.8	8.5 ± 6.5	2.75	.006
Depression, n (%)	69 (62)	62 (48)	4.28	.039

[a]All values are mean ± SD unless otherwise noted.
Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, NTFE = never-treated first-episode, PANSS = Positive and Negative Syndrome Scale.

(ANCOVA) was used, taking the HDRS-17 total score as the dependent measure, the sex (male vs female) and diagnosis (depression vs nondepression) as independent predictors, and age, education, body mass index (BMI), smoking, and age at onset as covariates. Main effects of sex, subclinical group (depression or nondepression), and the interaction of sex × subclinical group were tested. Further, in the male and female patient groups separately, ANCOVA was performed to compare the differences in the clinical parameters between depression and nondepression subclinical groups. In addition, Pearson correlation coefficients were calculated to assess the linear relationships between the variables, and Bonferroni corrections were used to adjust multiple tests. Finally, we conducted a stepwise multiple regression analysis to investigate the relationship between the HDRS-17 total score and the symptoms of psychosis assessed by the PANSS in male and female patients, respectively. All statistical analyses were conducted with SPSS version 15.0 (SPSS Inc, Chicago, Illinois). Data are shown as mean ± SD. All *P* values are 2-tailed, and the significance level is ≤ .05.

RESULTS

Sex Differences in Demographic Characteristics in NTFE Patients

As shown in Table 1, we found a significantly lower age, earlier age at onset, and higher smoking rate in male than in female patients (all $P < .05$). Moreover, male patients had significantly higher HDRS-17 total scores and PANSS general psychopathology, cognitive factor, and negative symptoms subscores and total scores than female patients (all $P < .01$).

In addition, we found significantly positive associations of the PANSS cognitive factor subscore with the PANSS total score ($r_{239} = 0.66$, $P < .0001$; Bonferroni-corrected $P < .01$), negative symptoms subscore ($r_{239} = 0.58$, $P < .0001$; Bonferroni-corrected $P < .01$), general psychopathology subscore ($r_{239} = 0.50$, $P < .0001$; Bonferroni-corrected $P < .01$), positive symptoms subscore ($r_{239} = 0.36$, $P < .0001$; Bonferroni-corrected $P < .01$), and HDRS-17 scores ($r_{239} = 0.22$, $P < .001$; Bonferroni-corrected $P < .01$).

In addition, while a previous study[45] has clearly demonstrated that more severe depressive symptoms are related to better illness insight, the so-called insight paradox, our correlation analysis showed no significant association between the insight item and HDRS-17 total score ($r_{1, 239} = 0.06$, $P = .35$).

Sex Differences in the Prevalence Rate and Clinical Features of Depressive Symptoms in NTFE Patients

Of male and female patients together, 54.6% met the criteria for comorbid depression (Table 1). Further analysis showed that the proportion of women with depressive symptoms (48.1%) was less than that of men (62.2%) ($\chi^2_1 = 4.28$, $P = .039$). Logistic regression analysis showed that this difference remained significant after adjusting for confounding factors such as age, education, smoking, and BMI ($\chi^2 = 4.12$, $P = .042$; adjusted OR = 0.576; 95% confidence interval (CI), 0.338–0.981).

Using multivariate ANCOVA, we did not observe a sex × diagnosis interaction effect on depression ($F = 2.08$, $P > .05$) (Table 2). In addition, data from the male and female schizophrenia patients were analyzed separately to examine sex differences in clinical features correlated with comorbid depressive symptoms. In male patients, the following clinical features were significantly different between patients with and without comorbid depressive symptoms: PANSS general psychopathology subscore ($F_{1, 109} = 18.86$, $P < .001$; Bonferroni-corrected $P < .01$), PANSS total score ($F_{1, 109} = 13.29$, $P < .001$; Bonferroni-corrected $P < .01$), and PANSS negative symptoms subscore ($F_{1, 109} = 5.43$, $P = .022$; Bonferroni-corrected $P > .05$). Using HDRS-17 total score as the dependent variable and sex, age, age at onset, and PANSS total score and subscores as the independent covariates, the results of stepwise multiple regression analysis showed that the PANSS general psychopathology subscale ($\beta = 0.75$, $t = 7.72$, $P < .001$) and PANSS total score ($\beta = 0.44$, $t = 4.81$, $P < .001$) can significantly predict the HDRS-17 total score.

Table 2. Demographic and Clinical Characteristics Between NTFE Schizophrenia Patients With and Without Depressive Symptoms, Grouped by Sex

	Male Patients[a] (n = 111)		Female Patients[a] (n = 129)				
Characteristic	Depression (n = 69)	Nondepression (n = 42)	Depression (n = 62)	Nondepression (n = 67)	Category *F* (*P* Value)[b]	Sex *F* (*P* Value)[b]	Category × Sex *F* (*P* Value)[b]
Age, y	26.2 ± 8.2	26.7 ± 8.7	29.8 ± 10.0	29.8 ± 10.1	0.04 (.85)	7.55 (.006)	0.03 (.85)
Education, y	12.3 ± 3.4	12.3 ± 4.1	12.1 ± 2.9	13.0 ± 4.0	0.82 (.37)	0.24 (.63)	1.08 (.30)
Body mass index	21.9 ± 3.9	22.4 ± 3.5	22.4 ± 3.9	21.5 ± 3.9	0.10 (.75)	0.19 (.66)	2.11 (.15)
Age at onset, y	24.3 ± 8.0	24.5 ± 8.5	28.2 ± 10.2	27.2 ± 9.7	0.11 (.74)	7.31 (.007)	0.24 (.62)
PANSS							
Positive symptom subscale	25.9 ± 7.4	25.4 ± 7.2	26.7 ± 6.4	24.6 ± 5.2[c]	2.19 (.14)	0.002 (.96)	0.85 (.36)
Negative symptom subscale	22.9 ± 9.1	18.9 ± 7.7[d]	19.0 ± 7.5	18.0 ± 6.1	5.88 (.016)	5.40 (.021)	2.11 (.15)
General psychopathology subscale	47.5 ± 13.2	37.5 ± 9.2[e]	43.0 ± 9.8	35.0 ± 5.6[f]	47.81 (.000)	7.37 (.007)	0.65 (.42)
Total score	96.3 ± 21.9	81.8 ± 17.2[e]	88.7 ± 18.1	77.6 ± 11.7[f]	29.99 (.000)	6.51 (.011)	0.55 (.46)
Cognitive factor	9.3 ± 4.4	8.0 ± 3.9	7.9 ± 3.3	6.6 ± 3.0[c]	7.25 (.008)	8.15 (.005)	0.01 (.91)
HDRS-17 total score	15.7 ± 8.4	4.0 ± 1.9[e]	13.4 ± 5.9	3.8 ± 2.1[f]	211.1 (.000)	2.82 (.09)	2.08 (.15)

[a]Values are mean ± SD.
[b]*P* values are 2-tailed and the significance level is .05.
[c]*P* < .05 significant difference between female patients with depression and nondepression.
[d]*P* < .05 significant difference between male patients with depression and nondepression.
[e]*P* < .001 significant difference between male patients with depression and nondepression.
[f]*P* < .001 significant difference between female patients with depression and nondepression.
Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, NTFE = never-treated first-episode, PANSS = Positive and Negative Syndrome Scale.

In addition, the logistic regression analysis indicated that the HDRS-17 total score was related to the following variables: the PANSS general psychopathology subscore (OR = 1.12; 95% CI, 1.05–1.19; Wald $\chi^2_1 = 13.0$, $P < .001$) and PANSS total score (OR = 1.05; 95% CI, 1.02–1.08; Wald $\chi^2_1 = 11.1$, $P = .001$).

In female patients, the following clinical features were markedly different between the patients with and without depressive symptoms: PANSS general psychopathology subscore ($F_{1,\ 129} = 32.79$, $P < .001$; Bonferroni-corrected $P < .001$), PANSS total score ($F_{1,\ 129} = 17.13$, $P < .001$; Bonferroni-corrected $P < .001$), PANSS cognitive factor subscore ($F_{1,\ 129} = 5.06$, $P = .026$; Bonferroni-corrected $P > .05$) and PANSS positive symptoms subscore ($F_{1,\ 129} = 4.06$, $P = .032$; Bonferroni-corrected $P > .05$). Using HDRS-17 total score as the dependent variable and sex, age, age at onset, and PANSS total score and subscores as the independent covariate, the results of multiple regression analysis revealed that the PANSS general psychopathology subscore ($\beta = 0.74$, $t = 8.45$, $P < .001$), the PANSS total score ($\beta = 0.47$, $t = 5.71$, $P < .001$), and the PANSS cognitive factor subscore ($\beta = 0.24$, $t = 2.60$, $P = .011$) can significantly predict the HDRS-17 total score. In addition, the logistic regression analysis showed that the HDRS-17 total score was correlated with the following variables: the PANSS general psychopathology subscore (OR = 1.23; 95% CI, 1.13–1.34; Wald $\chi^2_1 = 21.2$, $P = .000$), PANSS total score (OR = 1.05; 95% CI, 1.02–1.08; Wald $\chi^2_1 = 12.3$, $P < .001$) and PANSS positive symptoms subscore (OR = 1.05; 95% CI, 0.99–1.13; Wald $\chi^2_1 = 4.47$, $P = .034$).

DISCUSSION

Several main findings in this study include: (1) never-treated patients with first-episode schizophrenia had marked sex differences favoring women in age, age at onset, smoking, psychotic and depressive symptoms, and cognitive symptoms; (2) male NTFE patients displayed a significantly higher rate of co-occurring depression symptoms and greater depressive symptoms than female patients; and (3) sex differences were found in the correlation between HDRS-17 scores and clinical symptoms in NTFE patients.

Sex Differences in Clinical Profiles in NTFE Patients

As far as we know, this study is the largest to date assessing the sex differences in comorbid depressive symptoms of never-treated patients with first-episode schizophrenia. Our results showed sex differences in many aspects of schizophrenia patients, even in the early stage of illness. First, we found an earlier age at onset in male than female patients, which is in accordance with numerous studies[1,11,12] performed in various ethnic populations, although some studies[46,47] have reported there is no sex difference in the age at onset in patients with schizophrenia, while another showed a preponderance of early onset in women.[48] Second, we found male patients' smoking rate was significantly higher than female patients' (5% vs 49%); however, the smoking rates in male and female NTFE patients were similar to those in our previous report in young healthy controls,[1] suggesting that acute psychosis may not impact smoking rates in male or female patients. Third, we found more severe PANSS negative symptoms, general psychopathology, and total scores in male than female patients, favoring women. Previous studies[46,47] reported that female patients with chronic schizophrenia display milder negative symptoms than male patients, which is consistent with our present finding, suggesting that female sex may be protective to a certain level for negative symptoms both at the initial phase and in the long-term process of the illness course of schizophrenia. However, we did not find sex differences in PANSS positive symptoms, and some previous studies[1,47,49] even reported that female schizophrenia patients in both first-episode and chronic patients had more

positive symptoms. These findings indicate that female sex may not be a protective factor or may even be a harmful factor for positive symptoms. Inconsistent study findings of sex differences in clinical symptomatology may be related to differences in the stages of disease progression (first episode vs chronic), illness courses of patients, exposure to antipsychotic medications, sample size and representation (outpatients vs inpatients vs community), and other related parameters.

Interestingly, our current study observed a significantly lower PANSS cognitive factor score in female than male patients, suggesting that female patients may have better cognitive performance, which is consistent with many, but not all, previous results.[1,50] Female patients displayed better cognitive symptoms compared with male patients, suggesting that women may be protected from cognitive impairment associated with schizophrenia even at the early stage of illness. This protective effect from cognitive damage in female patients may also be correlated to their fewer clinical symptoms, especially negative or depressive symptoms, since a significant relationship was found between negative and depressive symptoms and poor cognitive performance.[51] Moreover, in the current study, we also found that the PANSS cognitive factor subscore was significantly associated with the PANSS general psychopathology subscore, PANSS negative symptoms subscore, and HDRS-17 total score (all $P < .001$).

Sex Difference in Depressive Symptoms and Its Clinical Correlates in NTFE Patients

We found a sex difference in the incidence rate of depressive symptoms in never-treated patients with first-episode schizophrenia, which was significantly higher in men than in women (62.2% vs 48.1%). Many studies[34–36,52] have indicated that the rate of co-occurring depression in women is higher than that of men, which has been confirmed in different ethnic groups. However, there has been no special study to explore the sex difference in the incidence and clinical relevance of depressive symptoms in schizophrenia patients. The previous 2 studies did not find a sex difference in comorbid depression in patients with chronic schizophrenia[53] or an acute exacerbation.[54] A recent study[55] investigated depressive symptoms assessed by the Calgary Depression Scale for Schizophrenia in patients of multiplex and simplex schizophrenia families, showing higher depressive symptoms in women and in the male multiplex group. Interestingly, a previous study[37] showed that among chronic ketamine users, women but not men showed increased depression scores. Another recent meta-analysis[38] did not show any sex-related difference in depression in individuals with overactive bladder. In our study, we observed that the incidence rate and severity of comorbid depressive symptoms were lower in female than male NTFE patients. This result contrasts with reports showing a higher rate of depressive symptoms or greater depressive symptoms in female than in male patients[34–36,52] or patients with physical illness.[37] We could not determine the reasonable mechanisms to explain these discrepant findings and speculate that schizophrenia patients may have specific psychopathological mechanisms that are different from those of patients with other psychiatric or physical diseases. Furthermore, the patients in our study were first-episode and drug-naïve with severe psychotic symptoms that differed from those of chronic patients reported in other studies, which may have a different pathophysiologic basis.

Further, we found that comorbid depressive symptoms were significantly correlated with the PANSS total score and PANSS general psychopathology subscore in both male and female patients, suggesting that depressive symptoms may be closely related to the total psychopathological symptoms. Since symptoms of comorbid depression abound in schizophrenia and are considered to be manifestations of schizophrenia spectrum disorders,[23,24] it is understandable that the depressive symptoms score was positively related with the PANSS total score and general psychopathology subscore in NTFE patients. Moreover, the PANSS general psychopathology subscale has some items that are directly related to the depressive symptoms.

Our current study further found that there is a sex difference in the relationship between comorbid depression and clinical parameters, indicating that in male patients, depressive symptoms were correlated with the PANSS general psychopathology and negative symptoms subscores and PANSS total score, while in female patients, depressive symptoms were correlated with the PANSS general psychopathology, positive symptoms, and cognitive factor subscores and PANSS total score. Moreover, we found that the depressive symptoms were more related to negative symptoms in men, but to positive symptoms in women.

Sex hormones may contribute to the sex differences in the relationship of co-occurring depressive symptoms and positive or negative symptoms in NTFE patients with schizophrenia. It is found that both estradiol and progesterone interact with several neurotransmitter systems, including dopamine, serotonin, norepinephrine, and acetylcholine,[56] with estradiol having a special impact on the dopaminergic system.[57] For example, a recent animal study showed that 17β-estradiol increased dopamine release in the dorsal striatum.[58] Further, progesterone modulated the estrogenic actions and exerted effects for the dopaminergic system.[57] In another recent animal experiment, estrogen treatment significantly increased the level of catalase and reduced lipid and nitrite levels in the substantia nigra and prefrontal cortex in Parkinson disease in mice.[59] In addition, the level of oxytocin in the ventral tegmental area affected sexual motivation and behavior by acting directly on dopaminergic neurons in mesolimbic and mesocortical areas[60] and locomotor activity,[61] suggesting that oxytocin may be involved in motivation and reward processes through the dopamine system. Taken together, these findings demonstrate close relationships between sex hormones and neurotransmitter systems, particularly in the mesolimbic dopaminergic system. On the other hand, it is believed that positive symptoms of schizophrenia are connected

with increased presynaptic striatal dopamine function, while negative symptoms are correlated with decreased adaptive transients of dopamine in the striatum for relevant stimuli,[62] suggesting the coexistence of these 2 disturbances of dopamine function in schizophrenia. In addition, it is well known that the dopaminergic system is involved in the neural mechanisms of both cognitive function and depression[63,64]; therefore, our findings of positive association of depressive symptoms with negative symptoms in male patients and with positive and cognitive symptoms in female patients may be correlated to differential levels of sex hormone, which may modulate dopamine release and function. However, these are only our speculations, and the exact interrelationships among sex hormone, dopamine, depression, and psychotic symptoms is worth further investigation.

The limitations of our study are as follows: First, a cross-sectional design was used, which could not form causal associations in sex, depressive symptoms, or psychotic symptoms in schizophrenia. Second, the patients in this study were acute inpatients with more severe psychiatric symptoms and a short period of illness, which limits the generalization of our findings to other patients such as outpatients, the patients in a community, or stable chronic patients. Third, the study was conducted only in a single psychiatric hospital from the Beijing area. Thus, the findings in this study should be replicated in other settings with different demographic and clinical characteristics before firm conclusions may be drawn. Fourth, with regard to cognitive tests, cognitive scores were extracted from the 5-factor model of the PANSS scores rather than from a specific cognitive test. These scores represent only a general evaluation of cognition, without any specific domain. Hence, the relationship between co-occurring depression and cognitive functions, especially in female patients, should be replicated applying a specific cognitive instrument in future research. Fifth, other variables that were not included in this study, such as physical exercise, suicide attempt history, and substance use except smoking, could have affected the absence or severity of depressive symptoms in NTFE patients. Sixth, on the basis of the inclusion criteria, we included only those patients between ages 16 and 45 years, which excluded those women experiencing a first-episode of psychosis during the perimenopausal period. Because the study of affective symptoms in schizophrenia may include populations at these ages, excluding these female patients could be considered a methodological limitation, which should be remedied in future studies. Seventh, in this study, we used the HDRS-17 as a rating scale to evaluate comorbid depressive symptoms; however, the HDRS-17 was not primarily developed to assess depressive symptoms in patients with schizophrenia. A more accurate depression instrument specially designed for schizophrenia, such as the Calgary Depression Scale for Schizophrenia,[55] should have been used, which may better differentiate depressive symptoms from other clinical symptoms, such as negative symptoms of schizophrenia.

In summary, our results showed that the incidence rate of co-occurring depression was significantly higher in male than in female NTFE patients, indicating a sex difference in the incidence of comorbid depressive symptoms at the early stage of schizophrenia. Moreover, male patients had significantly greater depressive symptoms shown on the HDRS-17 than female patients. In addition, we found significant sex differences in age, age at onset, smoking rate, and the PANSS general psychopathology subscores, cognitive factor subscores, negative symptoms subscores, and total scores in these NTFE patients. Further, we found sex differences in the correlations of co-occurring depressive symptoms with clinical parameters. Although the results show that depressive symptoms were correlated with the PANSS total score and general psychopathology subscore in both men and women, men showed some specific correlations of depressive symptoms with the PANSS negative symptoms subscore while women showed correlations with the PANSS positive symptoms subscore and cognitive factor subscores. These differential relationships in male and female patients are probably related to the role of sex hormones in the regulation of neurotransmitter systems, especially the dopamine system. However, due to some methodological limitations of this present study, our findings should be considered as preliminary and should be verified in a large sample size from different ethnic populations using a longitudinal and prospective design.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.