

Gender Differences in the First-Year Antipsychotic Treatment for Chinese First-Episode Schizophrenia

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

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Objective: To investigate the gender differences in the efficacy and side effects of three frequently used antipsychotic medicines (risperidone, olanzapine, aripiprazole) for patients with first-episode schizophrenia during the first year of treatment.

Methods: A total of 569 patients with first-episode schizophrenia were randomly assigned to risperidone, olanzapine, and aripiprazole groups. All patients were treated according to their actual clinical needs. Clinical efficacies were assessed by the Positive and Negative Symptom Scale (PANSS) and side effects were assessed by the Udvalg for Kliniske Undersogelser Side-Effect scale (UKU). All assessments were completed at baseline and at 1, 2, 3, 6, 9, and 12 months.

Results: Males had higher baseline PANSS total scores and PANSS negative and general pathological scores. No significant interactions were found between treatment time and gender in psychopathology improvements in all three groups. In the end of the first year, female patients receiving risperidone reported more dermatological symptoms (rashes) than males, female patients receiving olanzapine reported more autonomic side effects and dermatological symptoms than males, and female patients receiving aripiprazole reported more psychotic side effects than males.

Conclusion: Gender differences exhibited in response to antipsychotic treatments for Chinese patients with first-episode schizophrenia. After the first year of antipsychotic treatment, drug-related side effects were more likely presented in female patients than male patients.

Keywords: first-episode schizophrenia, gender difference, antipsychotic treatment, treatment response, side effects

Introduction

Gender differences generally present in schizophrenia, including but not limited to clinical characteristics, treatment responses, and the global functioning.¹ Female patients seem to have less hospitalization time, fewer functional impairments, and better social support than male patients.² Evidence suggested that female schizophrenic patients may have a more favorable clinical prognosis.^{3,4} However, gender differences in response to antipsychotic treatments have not been systematically investigated, especially in Chinese schizophrenic patients.

Generally, males have faster gastrointestinal absorptions, lower fat contents, and higher activity of metabolic enzymes than females. Thus, males need higher doses of antipsychotic drugs to reach stable blood concentration, which increases their risk of drug-related side effects.⁵ However, female schizophrenic patients have been observed to report more side effects, eg weight gain, sexual dysfunction, and

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arrhythmia than men.⁶ Clinical studies and animal studies suggested an antidopaminergic effect of estrogens,^{7,8} which accounted for some of the better responses to antipsychotics in females. In addition, gender differences were reported in responses to different types of antipsychotic drugs. Female patients receiving clozapine displayed significantly better prognosis than male patients, while olanzapine-related gender differences were only observed in quality of life. No gender differences have been found in patients receiving risperidone.⁹

Gender differences in the treatment of first-episode schizophrenia (FES) have been reported based on the European First Episode Schizophrenia Trial,³ while few studies from Asia or developing countries have been reported. We designed a one-year prospective cohort study to examine the efficacy and side effects of three frequently used antipsychotics (olanzapine, risperidone, aripiprazole) in Chinese Han FES patients. The aims of this study were to prospectively investigate gender differences in responses to antipsychotics and drug-related side effects. We hypothesized that female FES patients have better responses to antipsychotic drugs, while may present more drug-related side effects.

Methods

Study Design

This was a one-year prospective study. The specific study design and patient disposition were published elsewhere.¹⁰ All participants were aged 18–45 years and met the diagnostic criteria for schizophrenia according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorder-IV Axis I Disorder (SCID). All participants had not been exposed to continuous antipsychotic treatments longer than four weeks. All participants and their legal guardians provided written informed consent before any assessments. This study was approved by the ethics committees of Peking University Institute of Mental Health and was registered as an International Standard Randomized Controlled Trial (No. NCT01057849).

Treatment

Participants were randomly assigned to a risperidone (3–6mg/day), olanzapine (10–25mg/day), or aripiprazole (15–30mg/day) group. Participants who showed little benefit from the first group were permitted to a medication alteration process (selection restricted to olanzapine, risperidone, and

aripiprazole), which was only allowed in the first four weeks. Drug choices were made based on patients' actual needs and psychiatrists' clinical experiences. Oral benzhexol (2–6mg/day), promethazine (25–75mg/day), or lorazepam (0.5–1.5mg/day) were allowed to be prescribed if necessary.

Assessment

Clinical efficacy was assessed by the Positive and Negative Symptom Scale (PANSS). It is a 30-item structured scale which can be divided into the positive syndrome subscale (PPANSS), the negative syndrome subscale (NPANSS), and the general syndrome subscale (GPANSS).¹¹ Side effects were measured by Udvalg for Kliniske Undersogelser Side-Effect Scale (UKU), which assessed psychotic side effects, neurological side effects, autonomic side effects, and other side effects (eg, dermatological symptoms, sexual functions).¹² Social functioning was assessed by Personal and Social Performance Scale (PSP).¹³ All assessments were conducted by trained psychiatrists at baseline and after 1, 2, 3, 6, 9, and 12 months' treatments. All interviewers attended a 1-week training workshop prior to the study and reached a qualified consistency (intraclass correlation coefficients or kappa values higher than 0.75).

Data Analysis

Independent sample *t*-tests were used to analyze gender differences in psychopathological changes. Repeated ANOVA was performed for the three antipsychotic groups to determine gender differences in the treatment effects and drug-related side effects. Due to differences in the number of follow-up visits, the tracking time point was used as the internal variable, and gender was used as the subject variable in the repeated ANOVA. All *p*-values were two-tailed and at a significance level of ≤ 0.05 .

Results

Baseline Clinical Characteristics and Patient Disposition

A total of 569 patients (289 males and 280 females) were enrolled and randomly assigned to risperidone group (100 males and 90 females), olanzapine group (89 males and 96 females), and aripiprazole group (100 males and 94 females). Proportions of patients assigned to individual antipsychotics were not different between females and males. Females were older than males in the whole sample ($p < 0.01$) and in the risperidone group ($p = 0.04$). Initial

Table 1 Baseline Clinical Characteristics of All First-Episode Schizophrenia Patients

	Whole Sample (n=569)	Male (n=283)	Female (n=286)	p value	Effect Size
Age at study entry (95% CI)	25.0(24.4, 25.6)	24.18(23.44,24.92)	25.84(24.91,26.76)	<0.01	0.83
Patients disposition				0.66	0.38
Risperidone	190(33.4)	100(34.6)	90(31.1)		
Olanzapine	185(32.5)	89(30.8)	96(34.3)		
Aripiprazole	194(34.1)	94(33.5)	100(34.6)		
Psychopathology (95% CI)					
PPANSS	23.41(22.96–23.85)	23.74(23.08–24.41)	23.08(22.49–23.67)	0.14	0.63
NPANSS	21.09(20.48–21.71)	22.07(21.23–22.90)	20.13(19.24–21.02)	<0.01	0.36
GPANSS	41.79(41.14–42.45)	42.46(41.51–43.42)	41.13(40.23–42.03)	0.04	0.57
PANSS Total	86.30(85.1–87.5)	88.27(86.53–90.01)	84.34(82.63–86.05)	<0.01	0.56
PSP scores	41.58(40.50–42.67)	40.70(39.14–42.26)	42.45(40.95–43.96)	0.11	0.65

Note: Significant results are shown in bold.

Abbreviations: PPANSS, positive PANSS subscale score; NPANSS, negative PANSS subscale score; GPANSS, general PANSS, subscale score; PSP, Personal and Social Performance Scale; CI, confidence interval.

NPANSS, GPANSS, and total PANSS scores were significantly higher in males than females (Table 1).

Gender Differences in Psychopathology and Functioning Change in the Initial Year of Antipsychotic Treatment

Two hundred and six patients (75 from risperidone group, 59 from olanzapine group, and 72 from aripiprazole) fully completed the first-year antipsychotic treatment and all assessments. After first month treatment, a significant improvement in PPANSS was seen in males than females ($p=0.03$). After nine months of treatment, significant improvement was seen in males than females in NPANSS ($p=0.03$) – see Table 2.

Gender Difference in Response to Specific Antipsychotics and Drug-Related Side Effects in the Initial Year of Treatment

In the end of the first year treatment, drug doses were not significantly different between males and females (risperidone: 3.29 ± 1.42 mg for male and 3.15 ± 1.38 mg for female; olanzapine: 10 (5,15) mg for male and 15 (10,20) mg for female; aripiprazole: 16.85 ± 5.03 mg for male and 15.48 ± 6.84 mg for female, all $p > 0.05$). After one-year treatment, patients-reported side effects were not significantly different among three antipsychotic groups. No significant interactions were found between treatment time and gender in psychopathology improvements (PANSS total scores and

all PANSS subscale scores) in all three antipsychotic groups (Table 3, Figures 1–3). In the end of the first year, female patients receiving risperidone reported more dermatological symptoms (rashes), female patients receiving olanzapine reported more autonomic side effects and dermatological symptoms, and female patients receiving aripiprazole reported more psychotic side effects than males (Table 3).

Discussion

This was one of the largest cohort studies to investigate gender differences in responses to antipsychotics in Chinese FES patients. We evaluated gender differences in responses to three frequently used second-generation antipsychotics and drug-related side effects during the initial year of treatment. Though males seemed to have robust improvements in positive symptoms after one-month treatment and negative symptoms after nine months of treatment, we failed to find interaction between gender and treatment time in terms of the improvement of psychopathology. Female patients reported more drug-related side effects than male patients in all antipsychotic groups.

Evidence have reported gender differences of symptom presence among schizophrenic patients, with more negative and disorganization symptoms presented in males and more affective and atypical positive symptoms presented in females.^{14,15} Our results confirmed that males displayed more serious negative, and general symptoms than females, but failed to find gender

Table 2 PANSS and PSP Score Changes from Baseline (95% CI) – Comparison of Males and Females

	Males (n=97)	Females (n=109)	p value	Effect Size
After one month				
PPANSS	-11.55 (-12.79, -10.31)	-9.86 (-10.86, -8.85)	0.03	0.74
NPANSS	-6.15 (-7.20, -5.10)	-5.70 (-6.76, -4.63)	0.59	0.35
GPANSS	-15.51 (-17.16, -13.86)	-13.34 (-15.17, -11.51)	0.12	0.41
PANSS Total	-33.39 (-36.52, -30.26)	-28.74 (-31.81, -25.67)	0.07	0.41
PSP scores	19.31 (16.41, 22.22)	16.64 (14.21, 19.07)	0.27	0.02
After two months				
PPANSS	-13.89 (-15.17, -12.62)	-12.93 (-13.95, -11.92)	0.20	0.38
NPANSS	-8.90 (-10.24, -7.56)	-8.14 (-9.45, -6.83)	0.45	0.70
GPANSS	-18.98 (-20.74, -17.22)	-17.93 (-19.58, -16.28)	0.45	0.34
PANSS Total	-41.97 (-45.41, -38.52)	-38.96 (-41.98, -35.94)	0.25	0.36
PSP scores	25.68 (22.39, 28.98)	23.83 (21.23, 26.42)	0.54	0.27
After three months				
PPANSS	-14.98 (-16.19, -13.76)	-14.41 (-15.42, -13.40)	0.40	0.15
NPANSS	-10.27 (-11.70, -8.83)	-9.47 (-10.76, -8.17)	0.45	0.44
GPANSS	-20.54 (-22.24, -18.85)	-19.87 (-21.49, -18.26)	0.74	0.35
PANSS Total	-45.98 (-49.29, -42.67)	-43.74 (-46.61, -40.87)	0.42	0.19
PSP scores	29.52 (26.32, 32.72)	27.61 (25.19, 30.03)	0.29	0.46
After six months				
PPANSS	-15.46 (-16.64, -14.27)	-14.70 (-15.71, -13.71)	0.26	0.26
NPANSS	-10.71 (-12.36, -9.07)	-9.69 (-11.08, -8.29)	0.39	0.34
GPANSS	-21.64 (-23.26, -20.03)	-20.87 (-22.49, -19.25)	0.78	0.53
PANSS Total	-47.83 (-51.13, -44.52)	-45.17 (-48.17, -42.18)	0.31	0.52
PSP scores	32.26 (29.30, 35.22)	30.87 (28.38, 33.37)	0.48	0.55
After nine months				
PPANSS	-15.72 (-16.91, -14.54)	-14.68 (-15.69, -13.66)	0.11	0.29
NPANSS	-11.81 (-13.35, -10.27)	-9.73 (-11.09, -9.61)	0.03	0.42
GPANSS	-22.57 (-24.26, -20.87)	-21.51 (-23.13, -19.90)	0.53	0.38
PANSS Total	-50.15 (-53.40, -46.90)	-45.81 (-48.77, -42.84)	0.06	0.83
PSP scores	35.02 (32.01, 38.03)	32.95 (30.21, 35.69)	0.46	0.32
After one year				
PPANSS	-15.89 (-17.07, -14.72)	-14.90 (-15.92, -13.87)	0.14	0.44
NPANSS	-11.90 (-13.45, -10.36)	-10.21 (-11.66, -8.76)	0.16	0.13
GPANSS	-23.64 (-25.31, -21.97)	-22.01 (-23.68, -20.34)	0.34	0.51
PANSS Total	-51.47 (-54.68, -48.25)	-47.03 (-50.13, -43.92)	0.10	0.61
PSP scores	36.21 (32.88, 39.54)	36.04 (33.38, 38.70)	0.91	0.12

Note: Significant results are shown in bold.

Abbreviations: PPANSS, positive PANSS subscale score; NPANSS, negative PANSS subscale score; GPANSS, general PANSS, subscale score; PSP, Personal and Social Performance Scale; CI, confidence interval.

difference in positive symptoms. The Schizophrenia Outpatient Health Outcomes (SOHO) study and European First Episode Schizophrenia Trial have reported females responded better and more quickly to antipsychotics.^{3,9} Our results did not find gender differences in response to antipsychotic treatments. Inconsistent results may be related to differences in

selected antipsychotic medications. Although gender could be a predictor for antipsychotic efficacy, it may not be fit for all antipsychotic medications. The most significant gender differences were observed in typical antipsychotics and clozapine, while the efficacy of atypical antipsychotics seemed to not relate to gender.⁹

Table 3 Interaction Between Gender and Treatment Time in Psychopathology Improvement, Functioning Improvement, and Drug-Related Side Effects

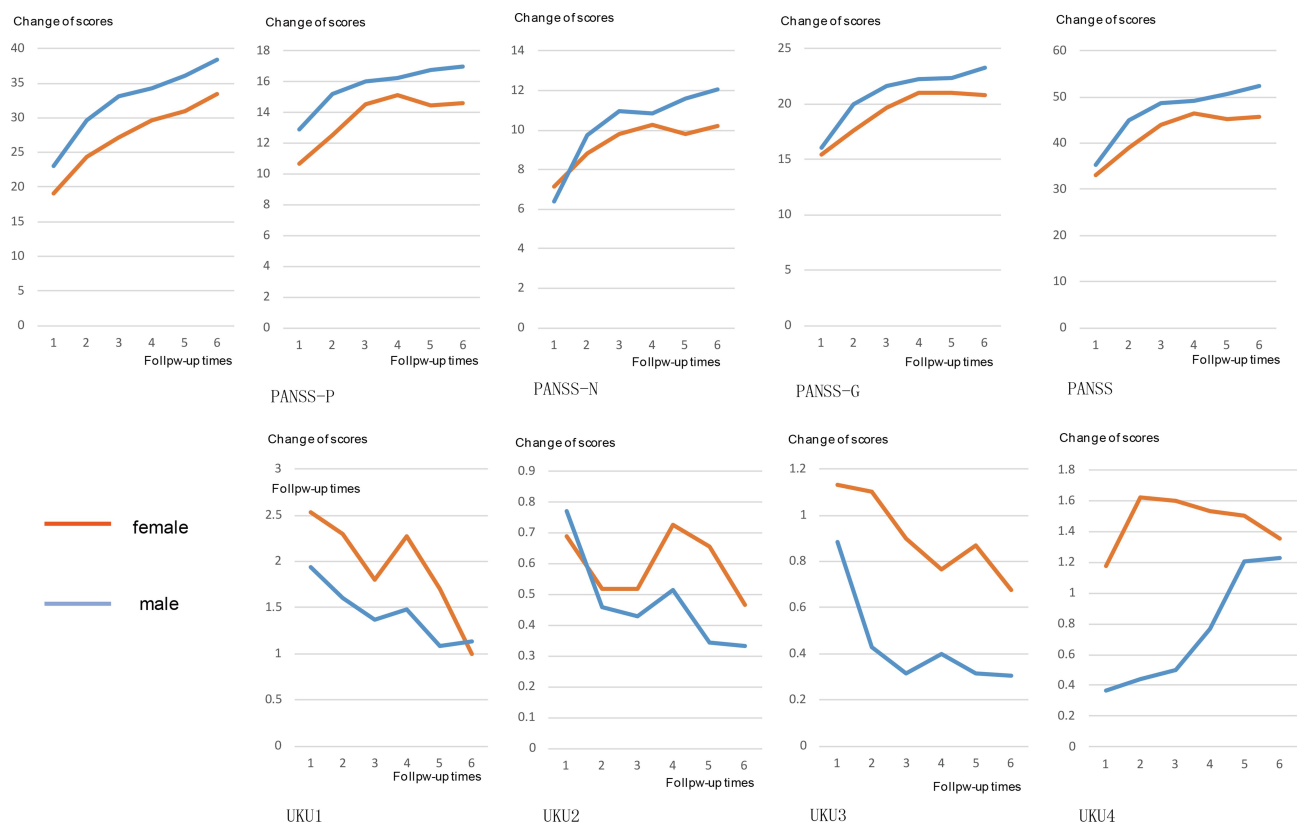
	Risperidone			Olanzapine			Aripiprazole		
	Ge	TP	Ge*TP	Ge	TP	Ge*TP	Ge	TP	Ge*TP
PPANSS	0.14	<0.01	0.47	0.54	<0.01	0.05	0.98	<0.01	0.99
NPANSS	0.53	<0.01	0.14	0.59	<0.01	0.92	0.39	<0.01	0.07
GPANSS	0.23	<0.01	0.39	0.49	<0.01	0.40	0.34	<0.01	0.50
PANSS_T	0.15	<0.01	0.47	0.98	<0.01	0.33	0.35	<0.01	0.43
PSP	0.12	<0.01	0.66	0.57	<0.01	0.45	0.86	<0.01	0.69
UKU1	0.12	<0.01	0.68	0.74	0.02	0.83	<0.01	0.06	0.07
UKU2	0.86	<0.01	0.46	0.14	0.26	0.83	0.11	0.02	0.47
UKU3	0.14	0.03	0.37	0.01	0.44	0.22	0.06	0.32	0.27
UKU4	0.03	0.03	0.12	0.04	<0.01	0.42	0.11	0.23	0.73

Note: All represent *p* values. Significant results are shown in bold.

Abbreviations: Ge, gender; TP, follow-up time; PPANSS, positive PANSS subscale score; NPANSS, negative PANSS subscale score; GPANSS, general PANSS subscale score; PANSS_T, total PANSS score; PSP, Personal and Social Performance Scale score; UKU1, psychotic side effect score; UKU2, neurological side effect score; UKU3, autonomic side effect score; UKU4, dermatological symptoms and sexual functions score.

Another explanation could be the high drop-off rate of our study, which is also an important limitation of this study. Cheng et al found that 47.1% of patients had discontinued using antipsychotics at the 52-week

follow-up, and reported treatment interruption was associated with gender.¹⁶ We found that more females completed the first year of antipsychotic treatment than males, though the difference was not statistically

**Figure 1** Symptoms and side effects changes after one-year risperidone treatment in first-episode schizophrenia - comparison of males and females.

Abbreviations: PANSS_P, positive PANSS subscale score; PANSS_N, negative PANSS subscale score; PANSS_G, general PANSS subscale score; PANSS_T, total PANSS score; PSP, Personal and social performance scale score; UKU1, psychic side effect score; UKU2, neurological side effect score; UKU3, autonomic side effect score; UKU4, dermatological symptoms and sexual functions score.

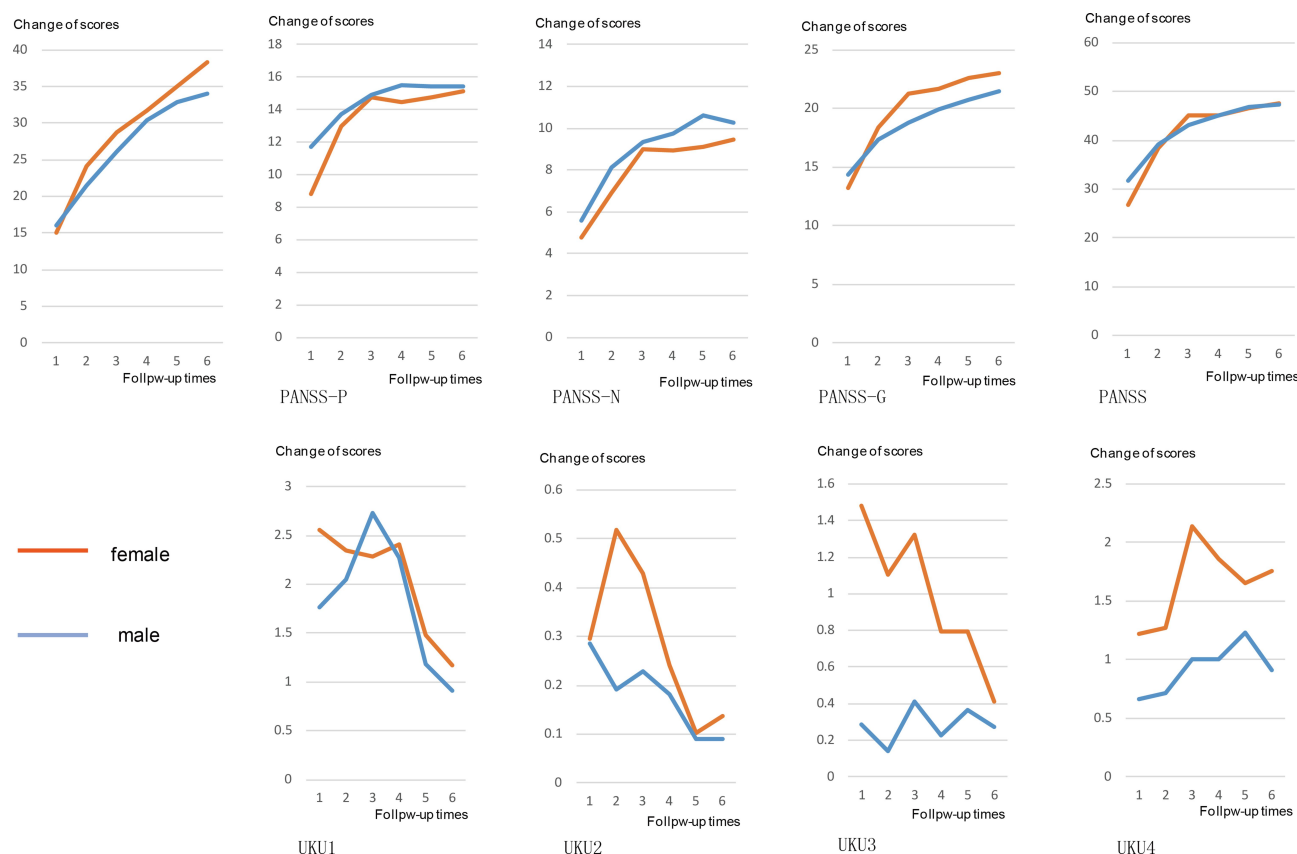


Figure 2 Symptoms and side effects changes after one-year olanzapine treatment in first-episode schizophrenia - comparison of males and females.

Abbreviations: PANSS_P, positive PANSS subscale score; PANSS_N, negative PANSS subscale score; PANSS_G, general PANSS subscale score; PANSS_T, total PANSS score; PSP, Personal and social performance scale score; UKU1, psychic side effect score; UKU2, neurological side effect score; UKU3, autonomic side effect score; UKU4, dermatological symptoms and sexual functions score.

significant. We failed to follow up the drop-offs and could not give more detailed results. Thus, we suggested that gender differences in response to specific treatments should be studied in expanded sample size.

Previous studies have reported that 50–75% higher rates of drug-related side effects occurred in females than in males,¹⁷ which is consistent with our results. Multiple factors may contribute to the gender differences in response to antipsychotic treatments, including the generally higher proportion of body fat in females and the differences in the metabolic pathways of drugs between genders.^{18,19} Additionally, self-reported side effects were more common in female patients,²⁰ which have been observed in both Western and Asian countries.²¹ Especially in Chinese culture, females are more concerned about their bodies, while men are more likely to ignore their feelings, which may also affect their self-reported side effects.

There are several limitations to this study. First, nearly half of the participants failed to complete the first year of treatment and were not included in final analysis, which may cause significant bias to our results. Second, though we measured drug-related side effects by UKU scale, reliable objective measures, such as prolactin and other plasma monitoring, were absent in this study. Self-reported side effects may also bias our results towards more side effects in females.

Conclusion

Gender differences exhibited in response to antipsychotic treatments for Chinese patients with first-episode schizophrenia. In the first year of treatment with risperidone, olanzapine, and aripiprazole, side effects were more likely presented in female patients than male patients. Gender should be taken into account in choosing appropriate antipsychotic treatment for patients. Gender differences are of importance and should be systematically investigated,

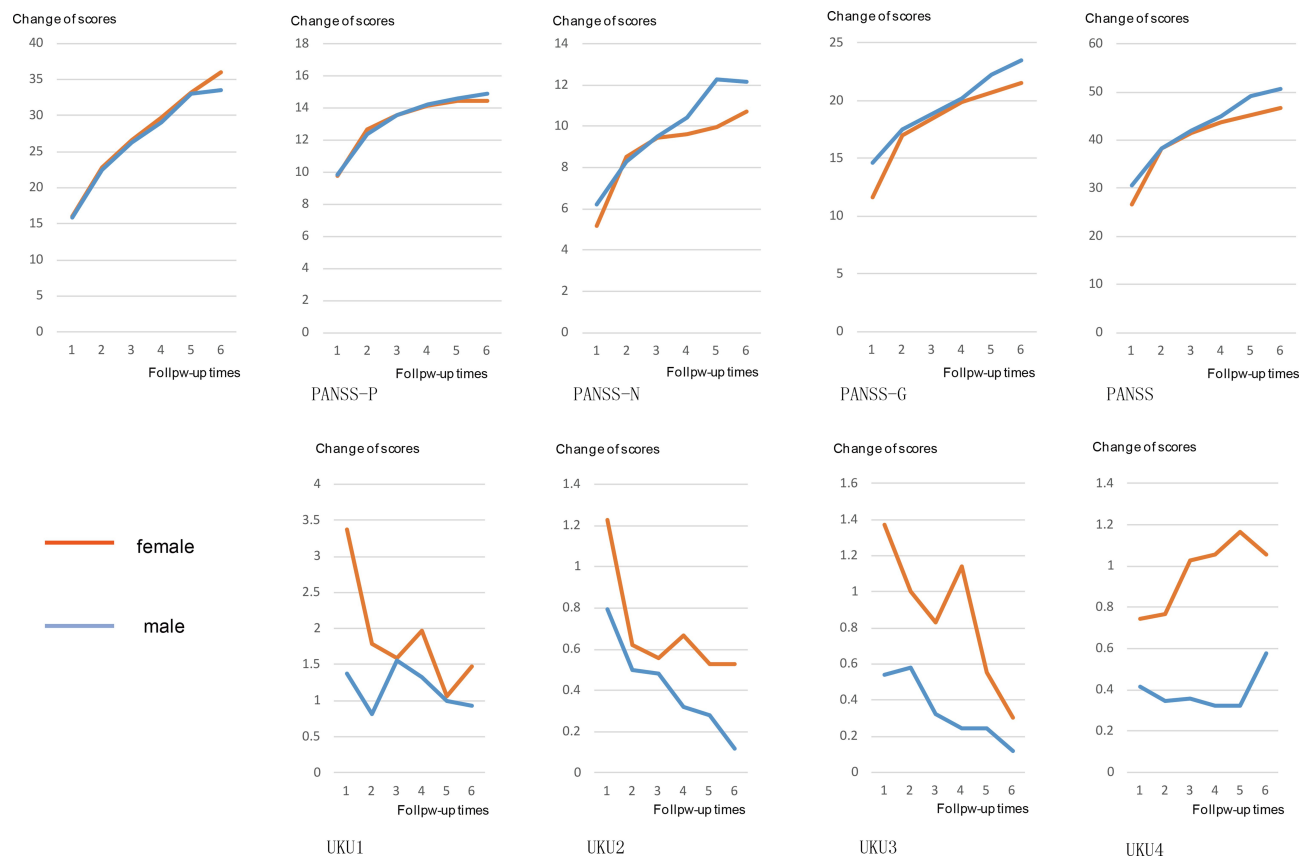


Figure 3 Symptoms and side effects changes after one-year aripiprazole treatment in first-episode schizophrenia - comparison of males and females.

Abbreviations: PANSS_P, positive PANSS subscale score; PANSS_N, negative PANSS subscale score; PANSS_G, general PANSS subscale score; PANSS_T, total PANSS score; PSP, Personal and social performance scale score; UKU1, psychic side effect score; UKU2, neurological side effect score; UKU3, autonomic side effect score; UKU4, dermatological symptoms and sexual functions score.

which may improve treatment outcomes and reduce side-effects, and contribute significantly to the development of precision treatment.

Data Sharing Statement

Data are available upon reasonable request. Data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments

This study was supported by National Key R&D Program of China (2018YFC1314200), the Capital's Funds for Health Improvement and Research (CFH, No.2018-4-4116), the Key Program of Beijing Science and Technology Commission (D171100007017002, D121100005012004), the National Key Project of Scientific and Technical Supporting Programs funded by Ministry of Science and Technology of China (no. 2007BAI17B04). Chengcheng Pu and Bingjie Huang are co-first authors for this study.

Disclosure

The authors declare no conflicts of interest.

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