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Original article

Real-world pharmacological treatment of patients with postpartum depression in China from 2016 to 2020: A cross-sectional analysis

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ABSTRACT

Objective: To determine the use and tendency of drugs for postpartum depression (PPD) in nine cities across China in 2016–2020 in order to provide a reference for drug use in the clinic.
Methods: The prescription data of drugs for PPD outpatients in nine cities (Beijing, Chengdu, Guangzhou, Harbin, Hangzhou, Shanghai, Shenyang, Tianjin and Zhengzhou) across China in 2016–2020 were extracted from the Hospital Prescription Analysis Cooperation Project database of the Hospital Pharmacy Professional Committee of Chinese Pharmaceutical Association. A cross-sectional analysis was then conducted of patient age, total prescription quantity, average prescription amount, defined daily doses (DDDs) of drugs, defined daily cost (DDC) of drugs and so on.
Results: In 2016–2020, more than half of PPD patients in these nine cities were distributed in first-tier cities (Beijing, Shanghai and Guangzhou), and were mainly aged 30–39 years. During the five-year period, the prescription quantity, total prescription amount and average prescription amount increased by 20.95%, 35.41% and 11.02%, respectively. In terms of prescription frequency and prescription amount, selective serotonin reuptake inhibitors (SSRIs) ranked first, followed by serotonin-norepinephrine reuptake inhibitors (SNRIs). With regard to DDDs, escitalopram, sertraline, paroxetine and venlafaxine ranked high, and sertraline was top year by year. The DDC of vortioxetine and milnacipran was greatest, while that of escitalopram, olanzapine and quetiapine declined sharply after being included in the China centralized drug-procurement program.
Conclusion: The number of PPD patients and the total prescription amount in the nine cities across China increased in 2016–2020. SSRIs and SNRIs were the main drugs for PPD treatment. Due to the national centralized drug-procurement policy, there has been a great reduction in the DDC, lightening the economic burden on patients.

1. Introduction

Postpartum depression (PPD) refers to depression occurring in the period after delivery in women (usually within four weeks), sometimes including depression continuing or relapsing after delivery. It was reported that the prevalence rate of PPD is 1.1–52.1% in China, with 14.7% on average (Expert group, 2014). PPD mainly has manifestations such as emotional irritability, irritability, insomnia, fatigue, anxiety, compunction, inability to take care of children, and suicidal thoughts, which may lead to the mother's suicide and infanticide in severe cases (Chen and Zhong, 2000). Currently, PPD is mainly treated by pharmacotherapy, psychotherapy and physical therapy. Of these, psychotherapy is the first-line treatment approach, which has a significant effect on PPD (Cui and Sui, 2005; Sriraman et al., 2015). For patients with severe symptoms or not receiving or refusing psychotherapy, antidepressant drugs are available options (Sriraman et al., 2015). Antidepressant drugs for PPD mainly include drugs resisting depression, anxiety and psychosis, as well as sedative-hypnotic drugs and mood stabilizers. As almost all antidepressant drugs will be found in breast milk to some extent, various factors should be taken into account when selecting these drugs for lactating mothers, and the selected drugs must be effective for the mother and safe for the baby. In addition, antidepressant drugs used by patients before

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delivery, target symptoms, drug allergy history, drug adverse reactions, and mother's willingness should also be considered, as the lack of medication compliance can easily lead to a relapse (Zhang et al., 2016). Therefore, appropriate drugs should be selected after comprehensive evaluation and weighing of the advantages and disadvantages. In this study, the prescribed drugs for PPD in nine cities over five years were analyzed to determine the current status of pharmacotherapy for PPD in China, to provide a reference for drug use in such patients, especially breastfeeding patients, and for pharmaceutical care offered by clinical pharmacists to such patients. The "Prescription Management Measures" issued by Decree No. 53 of the Ministry of Health of the People's Republic of China stipulates that prescriptions should follow the principles of safety, effectiveness and economy (Ministry of Health of the People's Republic of China, 2007), which is an important legal document for standardizing prescription management, improving prescription quality, promoting rational drug use and ensuring medical safety. Therefore, the economics of prescription were also evaluated to assess the cost of drugs for patients with PPD.

2. Data and methods

2.1. Data sources

The research data were obtained from the Hospital Prescription Analysis Cooperation Project of the Hospital Pharmacy Professional Committee of Chinese Pharmaceutical Association. In the Project, 121 sample hospitals in nine cities including Beijing, Chengdu, Guangzhou, Harbin, Hangzhou, Shanghai, Shenyang, Tianjin and Zhengzhou were included. The prescription data for 10 working days in each quarter (40 working days in 4 quarters and 200 working days in 5 years in total) were randomly selected through the information system of each hospital. Electronic information on outpatient prescriptions and inpatient medical orders over 10 working days in each quarter were summarized and included in the prescription database of the Hospital Prescription Analysis Cooperation Project.

2.2. Investigation methods

Outpatients prescription data containing the "Postpartum depression" field in the diagnosis (ICD10 code F53.002) in the nine cities in 4 quarters of each year (2016–2020) were extracted from the database, including prescription information such as prescription number, department, reimbursement status, drug generic name, trade name, drug specification, usage and dosage, drug quantity, drug unit price, prescription amount, patient gender, age and diagnosis. The exclusion criteria were prescriptions on drugs only for other diseases such as liver and gallbladder diseases, digestive tract diseases not PPD. The prescription data on drugs for depression used by PPD patients were then subjected to statistics and analysis.

For further analyses, we subdivided prescriptions into four age groups (18–29, 30–39, 40–49, over 50 years) and two regions (the first-tier cities, including Beijing, Shanghai and Guangzhou, and the non-first-tier cities, including Chengdu, Harbin, Hangzhou, Shenyang, Tianjin and Zhengzhou) (First-tier Cities Research Institute of China Business Network, 2021).

2.3. Evaluation criteria and methods

The analysis method with defined daily dose (DDD) as an indicator recommended by the World Health Organization (WHO) (ATC/DDD Index, 2021) was adopted. In this study, with DDD in the 2015 Clinical Medicine Guidelines of Pharmacopoeia of the People's Republic of China, WHO website data and drug instructions, prescription frequency, prescribed dosage and prescription amount were calculated by drug generic name, and the DDDs and defined daily cost (DDC) were calculated, sorted and analyzed. DDDs = the total annual prescribed dose of drugs / the DDD of drugs. The larger the DDDs, the higher the usage frequency of drugs in the clinic will be, reflecting the application trend of drugs in clinical practice. DDC = total annual prescription amount of drugs/DDDs of drugs, indicates the average daily cost of drugs, which is an index evaluating the total prescription amount and reflects the total price level of drugs. A larger DDC suggests a greater economic burden on patients.

2.4. Statistical analysis

We counted the types of medications used for PPD. Data classification and analyses were performed using Excel 2013 and Stata 15 software. We analyzed all the included prescriptions, and only the top ten drugs were selected when sorting the prescription frequency, prescription amount, DDDs and DDC for each single drug (Qi and Wang, 2001). Chi-square tests were used to compare demographic differences of patients, P values <0.05 considered as statistically significant. To avoid bias in data processing and analysis, all data were assessed by two pharmacists independently. A discussion was held with a third pharmacist to resolve any discrepancies during data evaluation (Wang et al., 2021).

3. Results

3.1. Demographic characters of patient

A total of 667 prescriptions for PPD in the nine cities in 2016–2020 were extracted from the database. After excluding unqualified prescriptions, 640 prescriptions for PPD were included, which showed an increase in the five years of 22.12%. Over half were distributed in the three first-tier cities Beijing, Shanghai and Guangzhou. The patient population aged 30–39 years was dominant, followed by the population aged 18–29 years. (Table 1).

3.2. Prescription frequency of various drugs for PPD

Among the various drugs for PPD in the nine cities during 2016–2020, the selective serotonin reuptake inhibitors (SSRIs) were prescribed with the highest frequency, followed by anti-anxiety agents (Fig. 1). Escitalopram, sertraline, paroxetine, olanzapine, venlafaxine, alprazolam and clonazepam ranked high. Of these, escitalopram was prescribed with the highest frequency since 2017 (Table 2).

3.3. Total prescription amount and average prescription amount of various drugs for PPD

The total prescription amount of various drugs for PPD increased from 25,700 yuan in 2016 to 34,800 yuan in 2020 in the nine cities, with an increase of 35.41% over these five years. The average prescription amount declined significantly from 2018, with a decrease of 8.97% compared with that in 2016, remained the same in 2019 compared with that in 2018, and rebounded in 2020, with an increase of 11.02% compared with that in 2016. Among the drugs used for PPD, SSRIs ranked first in terms of total prescription amount, followed by selective serotonin-norepinephrine reuptake inhibitors (SNRIs) (Fig. 2).The SSRI escitalopram ranked first in terms of total prescription amount in 2017–2019, followed by the SNRI venlafaxine, and the SSRI sertraline exhibited a continuous increase in total prescription amount in

Table 1
Demographic characters of patients (n = 640).

Subgroups	The year of 2016 (n = 104)	The year of 2017 (n = 144)	The year of 2018 (n = 114)	The year of 2019 (n = 151)	The year of 2020 (n = 127)	Total	Chi-square value	*P* value
Age group								
18–29 years	43	42	39	34	27	185	25.6871	0.012
30–39 years	56	79	55	90	80	360		
40–49 years	2	20	16	22	15	75		
Above 50 years	3	3	4	5	5	20		
Region								
First-tier cities	68	105	62	85	75	395	13.0924	0.011
Non-first-tier cities	36	39	52	66	52	245		

The *P* value of chi-square tests across subgroups.

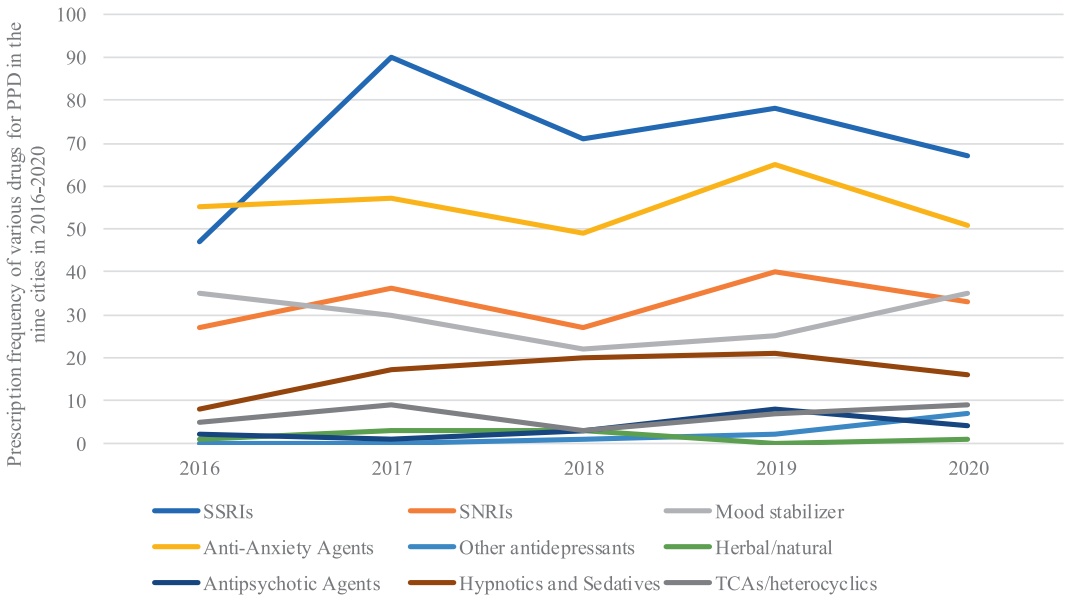

Fig. 1. Prescription frequency of various drugs for PPD in the nine cities in 2016–2020. Abbreviations: SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.

these years, and ranked second in 2020, surpassing venlafaxine (Table 3).

3.4. DDDs of various drugs for PPD

Among the various drugs for PPD in the nine cities studied in 2016–2020, the SSRIs escitalopram, paroxetine and sertraline and the SNRI venlafaxine ranked high in DDDs. Among them, the DDD of sertraline displayed a continuous increase, ranking first in 2020 (Table 4).

3.5. DDC of various drugs for PPD

With regard to DDC, quetiapine and olanzapine ranked top among the various drugs for PPD in the nine cities studied in 2016–2018. In 2019, vortioxetine and milnacipran were the top two in terms of DDC, while the DDC of olanzapine decreased significantly from 2019, and dropped from the top 10 in 2020, and that of quetiapine began to decline sharply in 2020 (Table 5).

4. Discussion

The Chinese family planning policy has been adjusted from the policy that "double-only-child couples can have two children" in November 2011 to the "two-child" policy, namely a couple can have two children, which was fully implemented in December 2015 (Zeng and Hesketh, 2016). As a result, the proportion of pregnant and lying-in women who have had one child is increasing in China. These women are more prone to unhealthy psychological problems such as anxiety and depression due to increased age, decline in physical function, higher probability of pregnancy complications and lower level of social support. PPD, a major postpartum complication, has attracted increasing attention (Lin and Cao, 2021). According to the American Psychiatric Association (APA) Guidelines for the Treatment of Depression (Practice guideline, 2010), PPD is mainly treated *via* psychotherapy, supplemented by drug therapy, and breast feeding of mothers taking antidepressant drugs during lactation is recommended. SSRIs are the first-line drugs for the treatment of PPD patients, and SNRIs and tricyclic antidepressants (TCAs) are also used for treating PPD. For severe PPD with other symptoms, antipsychotics, mood stabilizers, anti-anxiety agents and sedative-hypnotic drugs can serve as supplementary drugs. Drugs are selected mainly based on past medication history and tolerance. For breastfeeding women, the adverse effects of drugs on the infant should also be considered in drug selection, and safer drugs should be selected (Expert group, 2014). This study analyzed the prescriptions for PPD in nine cities over five years and found the current status of drug therapy for PPD in China.

Table 2
Top 10 Drugs for PPD prescription frequency in nine cities in 2016–2020.

2016			2017			2018			2019			2020		
Drug	Prescription frequency	%	Drug	Prescription frequency	%	Drug	Prescription frequency	%	Drug	Prescription frequency	%	Drug	Prescription frequency	%
Olanzapine	20	19.23	Escitalopram	45	31.25	Escitalopram	22	19.30	Escitalopram	33	21.85	Escitalopram	28	22.05
Escitalopram	19	18.27	Paroxetine	21	14.58	Sertraline	20	17.54	Venlafaxine	22	14.57	Sertraline	21	16.54
Venlafaxine	18	17.31	Olanzapine	20	13.89	Paroxetine	16	14.04	Sertraline	21	13.91	Olanzapine	21	16.54
Alprazolam	16	15.38	Venlafaxine	19	13.19	Venlafaxine	16	14.04	Tandospirone	16	10.60	Alprazolam	16	12.60
Clonazepam	15	14.42	Alprazolam	15	10.42	Olanzapine	14	12.28	Alprazolam	15	9.93	Mirtazapine	12	9.45
Sertraline	11	10.58	Clonazepam	14	9.72	Alprazolam	14	12.28	Duloxetine	13	8.61	Venlafaxine	11	8.66
Tandospirone	9	8.65	Sertraline	12	8.33	Clonazepam	12	10.53	Olanzapine	12	7.95	Lorazepam	11	8.66
Quetiapine	8	7.69	Mirtazapine	10	6.94	Dexzopiclone	10	8.77	Citalopram	11	7.28	Clonazepam	10	7.87
Flupentixol/ melitracen	7	6.73	Trazodone	8	5.56	Mirtazapine	7	6.14	Clonazepam	10	6.62	Zolpidem	10	7.87
Duloxetine	6	5.77	Fluoxetine	8	5.56	Zolpidem	7	6.14	Dexzopiclone	9	5.96	Trazodone	9	7.09
Citalopram	6	5.77	Zolpidem	8	5.56	–	–	–	Flupentixol/ melitracen	9	5.96	–	–	–

4.1. Demographic characters of patient

A phenomenological study of Chinese mothers showed that generally, PPD patients are willing to cope with PPD symptoms through self-help strategies such as talking with others, seeking help and thinking positively, and seeking professional help is not their first choice (Tang et al., 2021). The results of this study revealed that the rate of PPD visits was significantly higher in first-tier cities than that in non-first-tier cities this may be related to the education level, socioeconomic status or stigma towards mental illness of local citizens.

According to China's 2020 census, the average age of childbirth in China is 28.97 years (Office of the Leading Group of the State Council for the Seventh National Population Census, 2022), but the majority of patients with PPD in this study were above 30–39 years of age. The results seemed to indicate that PPD was probably more common in women of higher age, but the correlation between childbearing age and PPD is complex (Xiong and Deng, 2020). Recent study showed that among women with no history of depression, young mothers had an increased risk for PPD compared with mothers aged 25–29 years. They faced additional challenges for new mothers. Conversely, among those mothers with a depression history, women of advanced maternal age (>35 years) had an increased risk compared with mothers aged 25–29 years (Silverman et al, 2017). It cannot simply judged that women of advanced age are at higher risk for PPD. More research is needed to better understand the relationship between childbearing age and PPD.

4.2. Pharmacoeconomics evaluation

The sharp drop in the average prescription amount in 2018 may be related to the cancellation of drug price addition in public hospitals. In November 2016, the General Office of the State Council forwarded the Several Opinions of the medical system reform Leading Group of the State Council on Promoting and Deepening the Reform Experience of the Medical and Health System, in which it is clearly stated that all public hospitals should cancel the drug price addition. As of the end of September 2017, all hospitals in China had canceled the drug price addition, resulting in a significant reduction in drug costs. At the beginning of 2019, the policy of centralized drug procurement was gradually implemented in China, and olanzapine, escitalopram and quetiapine were successively included in the China drug centralized-procurement program (Joint Procurement Office, 2019); therefore, their prices were lowered. The ranking of their DDC declined after being included into the China drug centralized-procurement program in 2019, and dropped from the top 10 in 2020. In 2020, quetiapine was included in the China drug centralized-procurement program, and its DDC decline sharply in 2020. The above-mentioned drugs ranked top in usage frequency for the clinical treatment of PPD in the nine cities throughout the country. The decline in DDC also led to a decrease in the average prescription amount of drugs for PPD in these nine cities. However, the average prescription amount of drugs for PPD in the nine cities in 2020 began to rise. This may have been related to the COVID-19 pandemic in early 2020. In February 2020, the COVID-19 pandemic broke out in China. Under the blockade due to the pandemic, the medical needs of the people could not be met. For this reason, the General Office of the National Health Commission issued the Notice on Strengthening the Management of Medical Services During the Epidemic to Meet the Basic Medical Needs of the People, in which it is stipulated that for outpatients with chronic diseases, drugs can be prescribed for 12 weeks in a single prescription depending on the condition. Compared with the previous prescription, the average prescribed

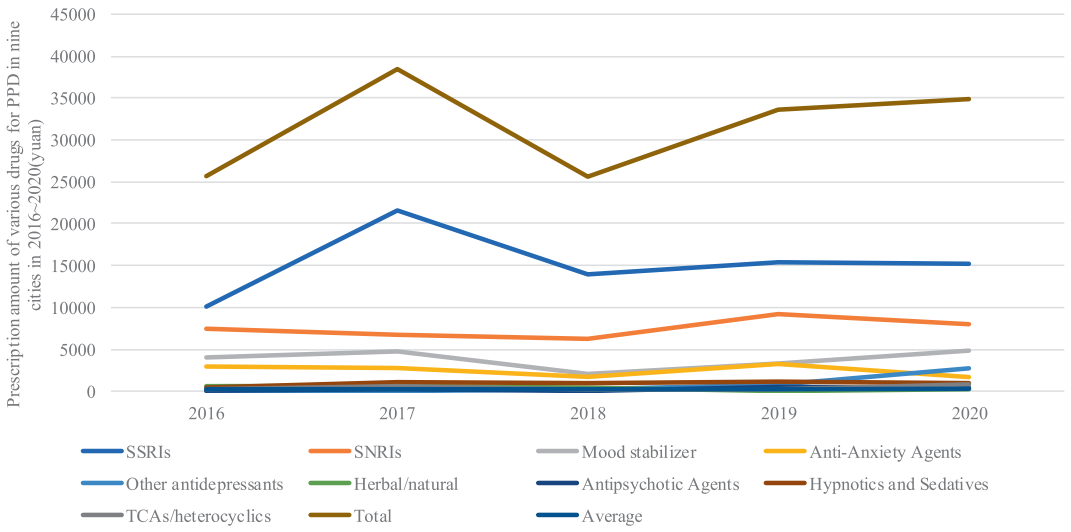

Fig. 2. Prescription amount of various drugs for PPD in nine cities in 2016–2020. Abbreviations: SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.

Table 3
Top 10 Drugs for PPD prescription amount in nine cities in 2016–2020.

2016		2017		2018		2019		2020	
Drug	Prescription amount(yuan)	Drug	Prescription amount(yuan)	Drug	Prescription amount(yuan)	Drug	Prescription amount(yuan)	Drug	Prescription amount(yuan)
Venlafaxine	5344.91	Escitalopram	12398.22	Escitalopram	5611.87	Escitalopram	8331.41	Escitalopram	5736.72
Escitalopram	5006.22	Venlafaxine	3900.33	Venlafaxine	4138.68	Venlafaxine	5235.67	Sertraline	5170.93
Olanzapine	2648.61	Fluoxetine	3631.53	Paroxetine	2999.2	Duloxetine	3303.44	Venlafaxine	3694.9
Tandospirone	1778.46	Olanzapine	3262.86	Sertraline	2686.04	Sertraline	3208.96	Olanzapine	3576.03
Sertraline	1258.04	Paroxetine	2838.76	Olanzapine	1486.2	Tandospirone	1988.3	Duloxetine	2598.2
Fluoxetine	1249.5	Sertraline	2140.71	Fluoxetine	1179.36	Olanzapine	1578.97	Fluoxetine	2039.1
Citalopram	1188.11	Tandospirone	1583.64	Duloxetine	1120.21	Citalopram	1481.84	Fluvoxamine	1636.2
Duloxetine	1030.18	Duloxetine	1530.54	Mirtazapine	981.48	Fluoxetine	1140.86	Agomelatine	1540
Mirtazapine	1008.7	Mirtazapine	1265	Tandospirone	972	Paroxetine	1108.18	Mirtazapine	1496.7
Paroxetine	709.16	Aripiprazole	951.2	Citalopram	783.44	Quetiapine	925	Vortioxetine	995.96

Table 4
Top 10 Drugs for PPD DDDs in nine cities in 2016–2020.

2016		2017		2018		2019		2020	
Drug	DDDs	Drug	DDDs	Drug	DDDs	Drug	DDDs	Drug	DDDs
Venlafaxine	491	Escitalopram	1024	Paroxetine	679	Escitalopram	982.5	Sertraline	1361
Escitalopram	401.5	Paroxetine	554	Sertraline	574	Sertraline	688	Escitalopram	900
Sertraline	210	Venlafaxine	420	Escitalopram	483.5	Venlafaxine	579.25	Venlafaxine	445.5
Alprazolam	206.4	Sertraline	388	Venlafaxine	420	Tandospirone	258.33	Olanzapine	414.5
Tandospirone	194	Fluoxetine	378	Alprazolam	157.6	Duloxetine	224.5	Fluoxetine	280
Clonazepam	187.5	St. John's wort (Hypericum perforatum)	225	Dexzopiclone	145	Paroxetine	204.25	Fluvoxamine	270
Citalopram	151	Tandospirone	204	Fluoxetine	140	Citalopram	202	Alprazolam	236
St. John's wort (Hypericum perforatum)	150	Zolpidem	190	Tandospirone	128	Alprazolam	188.4	Paroxetine	207.5
Olanzapine	134	Alprazolam	177.2	Citalopram	126	Zopiclone	174	Duloxetine	189
Fluoxetine	126	Olanzapine	140.5	St. John's wort (Hypericum perforatum)	120	Fluoxetine	140	Zolpidem	170

DDDs: defined daily doses = the total annual prescribed dose of drugs / the DDD of drugs.

dosage in a prescription increased significantly, resulting in the increased average prescription amount.

Prescriptions should follow the principles of safety, efficacy and economy. The policy of centralized drug procurement encourages preferential use of drugs which were included in the China drug centralized-procurement program, especially generic drugs that passed the consistency evaluation of the quality and efficacy. These drugs have the same high quality and strength as the brand-name drugs and are cheaper. In the first 5 batches of centralized procurement list, generic drugs accounted for 81.65%, and the maximum price drop after entering the list was 97.52% (Zhang et al., 2022). The National Healthcare Security Administration and other nine departments pointed out in the Implementation Opinions on Expanding the Scope of Pilot Areas for The Use of Centralized-procurement Drugs that the role of pharmacists should be strengthened in the evaluation of prescription dispensing

Table 5
Top 10 Drugs for PPD DDC in nine cities in 2016–2020.

2016		2017		2018		2019		2020	
Drug	DDC	Drug	DDC	Drug	DDC	Drug	DDC	Drug	DDC
Quetiapine	29.23	Quetiapine	39.59	Quetiapine	32.76	Vortioxetine	40.93	Vortioxetine	35.57
Amisulpride	24.24	Olanzapine	23.22	Olanzapine	22.18	Milnacipran	31.40	Milnacipran	35.20
Olanzapine	19.77	Aripiprazole	15.02	Duloxetine	16.85	Quetiapine	30.58	Amisulpride	15.52
Trazodone	16.14	Trazodone	14.56	Trazodone	14.01	Olanzapine	16.98	Trazodone	15.50
Duloxetine	13.92	Duloxetine	14.44	Agomelatine	13.00	Amisulpride	15.52	Quetiapine	14.31
Escitalopram	12.47	Risperidone	12.95	Escitalopram	11.61	Trazodone	15.49	Duloxetine	13.75
Oxazepam	12.03	Escitalopram	12.11	Oxazepam	11.18	Duloxetine	14.71	Agomelatine	12.22
Mirtazapine	11.21	Oxazepam	10.47	Venlafaxine	9.85	Agomelatine	13.00	Oxazepam	10.30
Venlafaxine	10.89	Mirtazapine	9.73	Mirtazapine	9.48	Oxazepam	10.70	Amfebutamone	10.20
Fluoxetine	9.92	Fluoxetine	9.61	Fluoxetine	8.42	Risperidone	9.85	Ziprasidone	10.20

DDC: defined daily cost = total annual prescription amount of drugs/DDDs of drugs.

(National Healthcare Security Administration et al., 2019). Pharmacists played an important role in providing policy interpretation and advice on rational drug selection (Zhang et al., 2021).

4.3. Drug characteristics

4.3.1. Analysis and assessment of the use of SSRIs and SNRIs

The total prescription amount of SSRIs ranked first, and the DDDs were highest, indicating that SSRIs are the first-line drugs for the clinical treatment of PPD in China, which is consistent with findings reported in the literature (Crescenzo et al., 2014; Stewart and Vigod, 2019). Most SSRIs have a milk concentration/maternal plasma concentration of less than 10%, and are almost undetectable in the blood of infants, so their use is safe during lactation (Sriraman et al., 2015). Sertraline is a commonly used SSRI for the treatment of PPD as its content in milk is too low to detect and it is relatively safe in pregnancy (Sriraman et al., 2015). Escitalopram, the active s-isomer of the antidepressant drug citalopram, has been proved in limited data to have no adverse effects on breastfed infants (Drugs and Lactation Database, 2021). It was discovered in a study of a population pharmacokinetic model of escitalopram and its main metabolites in patients with perinatal depression that the daily dose of escitalopram via breast milk in breastfed infants was 3.3% of the weight-adjusted dose in pregnant women (Weisskopf et al., 2016). Escitalopram and sertraline are the safest SSRIs for pregnant women, and paroxetine and sertraline are the first choices for breastfeeding women (Langan and Goodbred, 2016; Schoretsanitis et al., 2019; Orsolini and Bellantuono, 2015). Paroxetine is almost undetectable in the blood of breastfed infants, and its breast milk concentration/maternal plasma concentration is 5% (Oberlander et al., 2005). With the exception of sertraline, other SSRIs may increase the risk of hyperprolactinemia, thereby resulting in various complications including amenorrhea and osteoporosis (Goodnick et al., 2000). Due to its various characteristics, sertraline is outstanding among SSRIs and has become the most commonly used drug for PPD in the clinic.

Different from most other SSRIs, infant serum levels of fluoxetine exceeded 10% of the maternal level (Weissman et al., 2004). Its metabolite, norfluoxetine was also detected in infant serum, which has equal antidepressant activity to fluoxetine. Adverse effects such as colic, fussiness, and drowsiness have been reported in some breastfed infants (Drugs and Lactation Database, 2021). Previous studies showed that maternal postpartum fluoxetine treatment increased anxiety-like behavior and impaired hypothalamic–pituitaryadrenal (HPA) axis negative feedback in adult male off spring. It is unclear whether risking neonatal fluoxetine exposure outweighs potential therapeutic effects of fluoxetine (Sriraman et al., 2015; Gobinath et al., 2016).

The total prescription amount of SNRIs was second only to that of SSRIs. SNRI venlafaxine and its metabolites can enter breast milk, but the breast milk concentration/maternal plasma concentration is less than 10%; thus, it is relatively safe for pregnant women (Ilett et al., 2002). In addition, no obvious adverse reactions were found following clinical use of venlafaxine. However, research data on venlafaxine use in breastfeeding women are rare. Hence, venlafaxine should be used in breast-feeding women with caution, and infant sedation and weight gain should be monitored (Sriraman et al., 2015; Bellantuono et al., 2015). When the efficacy of SSRIs is unsatisfactory, SNRIs are ideal alternatives due to their low concentration in breast milk (Stewart and Vigod, 2019).

Milnacipran, a SNRI, shows no significant difference in efficacy and tolerability compared with other antidepressant drugs, and it has higher compliance due to its mild adverse reactions and low withdrawal rate than TCAs (Nakagawa et al., 2009). SSRIs are recommended as first-line drugs for depression in most clinical practice guidelines, but the inclusion of milnacipran as a first-line drug is recommended in one clinical practice guideline (Gabriel et al., 2020). Milnacipran has a low concentration in breast milk, but the safety data on its use in lactation are few; therefore, more data are required for verification (Drugs and Lactation Database, 2021). In addition, its price is relatively high. Milnacipran ranked second in DDC, but the prescription frequency in the clinic was low, with 1 prescription in Tianjin in 2019 at 7.85 yuan/tablet, and 2 prescriptions in Shanghai in 2020 at 8.8 yuan/tablet for a 25 mg/tablet.

4.3.2. Anti-anxiety agents

Most anti-anxiety agents are used in combination with antidepressant drugs. Anxiety symptoms are more common in PPD patients than in patients with major depressive disorder onset at other times. TCAs and SSRIs can aggravate anxiety symptoms or even cause panic disorder when used initially. Panic disorder can be relieved *via* auxiliary use of benzodiazepines. However, benzodiazepines have their own adverse effects and toxicity, including abuse and dependence. Therefore, in the APA guidelines, they are not recommended as primary drugs for patients with both depression and anxiety (Practice guideline, 2010). Considering that they exert sedative effects in infants, and the safety data on their use in lactation are scarce (Drugs and Lactation Database, 2021), they can be used for PPD only after careful consideration.

4.3.3. Other drugs

Olanzapine and quetiapine, mainly used for the treatment of PPD with bipolar disorder, were ranked top in DDC. They are regarded as first-line drugs in antipsychotic treatment, and their breast milk concentration/maternal plasma concentration is relatively low; thus, their short-term use in breastfeeding is relatively safe. However, breastfeeding also requires careful consideration of

possible mood instability as a result of sleep disruption. Frequent awakenings for breastfeeding purposes and consequent lack of sleep may increase the risk of relapse in women with bipolar disorder (Sharma et al., 2020). Considering mothers with bipolar disorder who may be at a particularly high risk of induction of mania or psychosis, breastfeeding should be prohibited in bipolar disorder women with a particularly high risk of mania or psychosis (Pacchiarotti et al., 2016; Sharma et al., 2017).

Vortioxetine is used to treat depression in adults, and was launched at the end of 2017 in China. Vortioxetine, unlike traditional antidepressant drugs, exerts antidepressant effects through multiple mechanisms and is also capable of improving patient cognition. Previous studies have reported that vortioxetine shows no significant difference in efficacy and safety compared with sertraline, and has weaker efficacy and fewer side effects than duloxetine (Borhannejad et al., 2020; Weisskopf et al., 2016; Koesters et al., 2017; Gonda et al., 2019). Vortioxetine can be secreted into breast milk, and there are few safety data on its use during lactation. A small sample study reported that the breast milk concentration/-maternal plasma concentration of vortioxetine was less than 10%, and no adverse events were reported during its use in lactation (Marshall et al., 2021). It was discovered in this study that vortioxetine was prescribed once each in 2019 and 2020 in Shanghai, the price was 40.93 yuan/tablet and 35.57 yuan/tablet, and the specification was 10 mg/tablet. Due to the high price, vortioxetine ranked first in DDC, but its prescription frequency is currently low in the clinic. In the case of increased clinical prescriptions, more patients will bear an economic burden.

5. Limitations

There were a few limitations in our study. First, since the prescription data were randomly selected for 10 working days in each quarter, it might not fully reflect the reality. Second, our analysis was conducted based on prescription data only containing the "Postpartum depression" field in the diagnosis. Prescription data containing the "depression" but no "postpartum" field in the diagnosis were excluded. Therefore, some prescription for patients with PPD might be also excluded due to the incomplete diagnosis. Finally, limited information on prescription data and lack of patient medical history limited the evaluation of rationality.

At present, the safety research data of many antidepressant drugs for maternal and infants is limited. Patient medication compliance and the adverse effects of drugs on the infant require long-term follow-up of patients and more drug safety studies. Reducing the economic burden of patients' medication is also a long-term project. Whether the implementation of national policies is effective and whether it can reduce the economic burden on patients and ensure the safety and effectiveness of medication for patients still requires more research and discussion.

6. Conclusion

According to the investigation and analysis of the use of drugs for PPD in the nine cities in China in 2016–2020, the state has played a positive role in reducing the cost of drugs for PPD by abolishing drug price addition and implementing the policy of centralized drug procurement. Drugs with high prescription frequency and high amounts can be considered for inclusion in the centralized-procurement program, which has greater potential to reduce the economic burden on patients. It can be used as a reference to reduce drug prices and ensure drug affordability. Currently, SSRIs and SNRIs are the main drugs for PPD in clinical practice. The traditional drugs escitalopram, sertraline and venlafaxine are main choices for clinical treatment of PPD due to their efficacy, high safety and low economic burden. Of these, sertraline is currently the most commonly used in clinical practice. In terms of anti-anxiety agents, novel antidepressant drugs, and mood stabilizers, more studies should be conducted on the rationality of their use in PPD as the research data on their safety during postpartum lactation are limited. Our findings is in line with domestic and international guidelines and might be useful for the safe and rational use of drugs for PPD in clinical practice.

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Author contributions

All the authors contributed to the study conception and design. Xianli Wang and Kai Sun performed the study and analyzed the data. Kai Sun wrote the paper. Xianli Wang provides guidance for this study, critically revised the paper and approved the final version to be published.

Data sharing statement

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

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Statement of Ethics

The study conformed to the Guide of Hospital Prescription Analysis Cooperation Project database of the Hospital Pharmacy Professional Committee of Chinese Pharmaceutical Association.

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