Critical evaluation of paliperidone in the treatment of schizophrenia in Chinese patients: a systematic literature review

Background: Paliperidone (9-hydroxyrisperidone), the major active metabolite of risperidone, has been introduced as a novel atypical antipsychotic agent in many countries. It is available both as an oral extended-release (ER) formulation and as a long-acting injection (paliperidone palmitate, PP), which have been approved for treating schizophrenia in the People’s Republic of China since 2009 and 2012, respectively. This systematic review summarizes the efficacy, effectiveness, and safety of paliperidone in the treatment of schizophrenia in the Chinese population.

Methods: A systematic literature search was conducted on the databases covering international and Chinese core journals, published from January 1, 2008, to May 22, 2015.

Results: A total of 122 publications were retrieved, of which 63 studies were identified for inclusion; most studies were related to paliperidone ER (n=53), nine were related to PP, and one study was related to both agents. Paliperidone ER demonstrated at least comparable efficacy with active comparators, including risperidone, olanzapine, ziprasidone, or aripiprazole, and was found to be superior with respect to the onset of action and improvement in the Personal and Social Performance Scale score. Paliperidone ER appeared to be associated with a lower risk of metabolic syndromes; the most common treatment-emergent adverse events were extrapyramidal symptoms, akathisia, insomnia, and somnolence. Results from interventional and observational studies showed that PP was also an effective and well-tolerated treatment for Chinese patients with schizophrenia. The findings were generally consistent with those observed in non-Chinese populations.

Conclusion: Both paliperidone ER and PP were effective and well-tolerated agents for the treatment of schizophrenia in the Chinese population according to the data we reviewed. No new safety signals specific for the Chinese population were raised for paliperidone. Further studies may be needed to collect more data on long-term treatment of schizophrenia in the People’s Republic of China.

Keywords: paliperidone, antipsychotics, efficacy, effectiveness, safety

Introduction

Schizophrenia is one of the most common psychotic disorders. The 1-month prevalence of schizophrenia in the mainland Chinese population is 0.78% according to an epidemiologic study conducted in four provinces.1 Antipsychotics have been the mainstay of treatment for schizophrenia.

Paliperidone, also referred to as 9-hydroxyrisperidone, is the major active metabolite of risperidone.2 The mechanism of action of paliperidone is unknown; however, it is known that it acts as an antagonist at dopamine-2 (D₂) receptors and 5-hydroxytryptamine 2A (5-HT₂A) receptors, with a higher affinity for 5-HT₂A receptors.
than for D₂ receptors. In addition, paliperidone also acts as an antagonist at α₁-adrenoceptors, and binds with lower affinity to α₂-adrenoceptors and histamine-1 receptors. It has no affinity for cholinergic muscarinic receptors.³ Paliperidone is available as two extended-release (ER) formulations: an osmotic-controlled-release oral delivery system (Paliperidone ER, Invega), and an injectable suspension formulation of paliperidone palmitate (PP, Sustenna®). Paliperidone ER utilizes osmotic-controlled-release oral delivery system (OROS®) technology to provide sustained release over a 24-hour period, thereby reducing fluctuations in peak and trough plasma concentrations.⁴ It is administered once daily without initial dose titration, and was introduced in the People’s Republic of China in 2009 for the treatment of schizophrenia. PP is the first monthly long-acting injectable atypical antipsychotic agent in the People’s Republic of China.⁵ It was marketed in 2012, also indicated for schizophrenia. At present, these two formulations of paliperidone are in wide use in clinical practice in the People’s Republic of China.

There have been some studies evaluating the pharmacokinetic characteristics and clinical profiles of both paliperidone formulations in the Chinese population. The aim of our systematic review is to summarize the clinical evidence of the pharmacokinetic characteristics, efficacy, effectiveness, and safety of paliperidone in treating schizophrenia in the People’s Republic of China.

Methods
Data search
PubMed, Embase, and Cochrane Library databases and the Cochrane Controlled Trials Register of paliperidone ER or PP for schizophrenia in Chinese population were searched, as well as Chinese databases of China National Knowledge Infrastructure (CNKI) (http://www.cnki.net), Wanfang data (http://www.wanfangdata.com.cn) and CBM/VIP information (http://www.cqvip.com). The search included all clinical studies published between January 1, 2008, and May 22, 2015 (search date), supplemented by hand search of academic dissertations and several key literature sources. The search was conducted using several types of key terms, categories of country or region, disease classification, and treatment. For the category of country or region, the key terms were “China”, “Chinese”, “Taiwan”, “Taiwanese”, and “Hong Kong”. For the category of disease classification, the search term was “schizophrenia”. For the category of treatment, the key terms were “paliperidone”, “9-OH risperidone”, “Invega”, and “Sustenna”. For all the databases, search terms within each category were combined by using the Boolean operator OR. Categories were then combined by using the Boolean operator AND.

Study selection
Chinese language studies included in this review were restricted to the Chinese core medical journals, based on the Guide of Core Journal of China (2011 version) published by Peking University Press. The study participants were residents of the People’s Republic of China, Taiwan, or Hong Kong, with a diagnosis of schizophrenia by any criteria, irrespective of age or sex. The types of intervention were paliperidone ER or PP. The included studies also had to report numerical data on at least one recognized outcome measure related to efficacy, effectiveness, or safety/tolerability. Studies were excluded if they were duplicate publications, or had no numerically reportable data on at least one relevant outcome measure. Case reports, narrative reviews, editorials, letters to the editor, or publications that did not include any formulation of paliperidone as the intervention were also excluded.

Results
Results of the search
A total of 122 publications were retrieved from the literature databases (Figure 1). Sixty of these were excluded because they did not meet the criteria of study selection. In addition, a publication about the pharmacokinetics of paliperidone ER conducted in healthy Chinese subjects, which was omitted in the initial electronic search, was added manually. A total of 63 publications were finally included in the review. Detailed information of the 63 publications are cited in Supplementary material.

Characteristics of the studies
Among the 63 publications included in the review, 53 were related to paliperidone ER, nine were related to PP, and one study compared paliperidone ER and PP. Most paliperidone ER-related publications were interventional studies, including 34 randomized controlled trials (RCTs) and 17 open-label, single-arm studies. Of the two nonintervention studies, one was observational, and the other a pharmacokinetic study. Of the nine PP-related studies, four were RCTs, three were observational studies, and two studies assessed the pharmacokinetics of PP in patients with schizophrenia.

These publications were published in either international peer-reviewed journals (publications in English, n=15) or Chinese core journals (publications in Chinese, n=48).

Paliperidone ER
Pharmacokinetic characteristics
Only one study had been performed to assess the pharmacokinetics of paliperidone ER in healthy Chinese subjects.⁷
This was a single-center, double-blind, randomized, single-dose study. A total of 24 healthy Han Chinese subjects (13 men, eleven women), aged 19–35 years, were randomly assigned in a 1:1 ratio to receive either paliperidone ER 3 or 9 mg. Mean $t_{\text{max}}$ and $t_{1/2}$ were 22.2 and 22.8 hours for the 3 mg group, and 24.8 and 21.4 hours for the 9 mg group. Similar to the pharmacokinetic data reported for the Caucasian population, the pharmacokinetics of paliperidone ER in the Chinese population can be adequately described by a one-compartment pharmacokinetic model, and is linearly related to dose. Based on these data, paliperidone ER is suitable to be taken once daily in the morning.

**Efficacy outcomes**

The efficacy of paliperidone ER in Chinese patients was assessed in 35 comparative studies (Table 1) and 17 single-arm studies. All the drugs used for comparison were atypical oral antipsychotics, mostly risperidone (n=13) and olanzapine (n=9), followed by aripiprazole (n=3), ziprasidone (n=2), and clozapine (n=2).

The mean change in Positive and Negative Syndrome Scale (PANSS) total scores compared with baseline was the most commonly reported symptom outcome. The overall findings from comparative studies and single-arm studies were consistent: paliperidone ER treatment was associated with statistically significant reductions in PANSS total scores.
### Table 1: Efficacy of paliperidone ER in comparative studies

| References | Blind | Treatment arms | Dose (mg/d) | Number of patients (enrolled) | Duration (weeks) | Mean change (% reduction versus baseline) | P-value | Response rate (%) | Remarks |
|------------|-------|----------------|-------------|-----------------------------|-----------------|-------------------------------------------|---------|-------------------|---------|
|            |       |                | BPRS        | PANSS                       |                 |                                           |         |                   |         |
| **Risperidone** |       |                |             |                             |                 |                                           |         |                   |         |
| Liu et al¹¹ | OL    | Paliperidone ER | 6.60        | 3–9                         | 25              | 8                                         |         | −38.80∗∗ (42.23) | NS      | 80%             |
| Risperidone       |       |                | 4.40        | 1–6                         | 25              | −36.80∗∗ (40.51)                           |         | 76%             |
| Li et al¹⁷        | NR    | Paliperidone ER | 6–12        | 48                          | 12              | −34.7∗ (36.37)                             | <0.05   |                   |         |
| Risperidone       |       |                | 2–6         | 62                          |                 | −26.4∗ (27.16)                             |         | 64%             |
| Su et al⁴⁶        | OL    | Paliperidone ER | 6.3         | 3–12                        | 47              | 12                                         |         | −41.6∗ (48.54)   | <0.05   | 60%             |
| Risperidone       |       |                | 3.8         | 1–6                         | 45              | −32.8∗ (38.41)                             |         | 66%             |
| Ren et al²⁶       | NR    | Paliperidone ER | 3–9         | 76                          | 4               | −48.73∗ (54.53)                            | <0.05   |                   |         |
| Risperidone       |       |                | 1–6         | 79                          |                 | −39.15∗ (44.44)                            |         | 68%             |
| Zhou et al²⁸      | NR    | Paliperidone ER | 3–12        | 38                          | 8               | −59.77∗∗ (57.38)                           | NS      | 82.9%           |
| Risperidone       |       |                | 2–6         | 38                          |                 | −43.23∗∗ (41.69)                           |         | 86.5%           |
| Na et al²⁰        | OL    | Paliperidone ER | 6           | 40                          | 8               | −39.7∗ (47.26)                             | NS      | 62.5%           |
| Risperidone       |       |                | 1–4         | 40                          |                 | −41.3∗∗ (48.88)                            |         | 67.5%           |
| Li et al⁴⁹        | NR    | Paliperidone ER | 8.32        | 3–12                        | 14              | 6                                         |         | −37.86∗∗∗ (43.52)| NS      | 70%             |
| Risperidone       |       |                | 5.86        | 1–6                         | 20              | −36.60∗∗∗ (42.29)                          |         | 66%             |
| Zhang et al⁴⁰     | NR    | Paliperidone ER | 9           | 3–12                        | 47              | 6                                         |         | −28.2∗ (34.60)   | NS      | 70%             |
| Risperidone       |       |                | 5           | 2–6                         | 47              | −27.4∗ (33.91)                             |         | 66%             |
| Yuan et al⁵¹      | NR    | Paliperidone ER | 8.9         | 3–12                        | 45              | 6                                         |         | −38.42∗ (41.10)  | NS      | 65%             |
| Risperidone       |       |                | 4.9         | 1–6                         | 45              | −37.46∗ (39.49)                            |         | 65%             |
| Li et al⁵²        | OL    | Paliperidone ER | 6.67        | 3–9                         | 40              | 8                                         |         | −38.37∗∗ (44.45)| NS      | 67.5%           |
| Risperidone       |       |                | 4.32        | 1–6                         | 40              | −36.88∗∗ (42.90)                           |         | 65%             |
| Deng et al⁵³      | OL    | Paliperidone ER | 8.76        | 6–12                        | 38              | 6                                         | −28.37 (57.52) | NS      | 94.74%          |
| Risperidone       |       |                | 5.42        | 4–8                         | 38              | −29.73 (58.48)                             |         | 92.11%          |
| Liu et al⁴⁶       | DB    | Paliperidone ER | 5.8         | 45                          | 8               | −44.26 (54.19)                             | <0.05   |                   |         |
| Risperidone       |       |                | 4.2         | 45                          |                 | −41.47 (51.31)                             |         | 84%             |
| Wang et al¹⁸      | OL    | Paliperidone ER | 6–12        | 41                          | 12              | −43.3∗ (46.31)                             | <0.05   |                   |         |
| Risperidone       |       |                | 1–8         | 40                          |                 | −23.2 (25.27)                              |         | 65%             |
| Xiong et al⁵⁵     | OL    | Paliperidone ER | 5.49        | 3–9                         | 127             | 8                                         | −28.4 (42.01) | <0.05   | 80.3%           |
| Risperidone       |       |                | 1–4         | 139                         |                 | −24.0 (35.98)                              |         | 74.8%           |
| **Olanzapine**    |       |                |             |                             |                 |                                           |         |                   |         |
| Hu et al⁵¹        | OL    | Paliperidone ER | 7.55        | 40                          | 12              | −20.33∗∗∗ (25.57)                          | NS      |                   |         |
| Olanzapine        |       |                | 15.87       | 40                          |                 | −23.39∗∗∗ (31.63)                          |         | 73%             |
| Zhu et al⁵⁴       | NR    | Paliperidone ER | 10.1        | 3–12                        | 15              | 12                                         |         | −30.87∗ (34.62)  | NS      | 67%             |
| Olanzapine        |       |                | 14.6        | 5–20                        | 15              | −26.25∗ (29.42)                            |         | 73%             |
| Xie et al⁵⁶       | OL    | Paliperidone ER | 6.4         | 3–12                        | 40              | 12                                         | −35.60∗ (41.21)| NS      | 85.7%           |
| Olanzapine        |       |                | 17.5        | 2.5–20                      | 40              | −38.59∗ (43.45)                            |         | 87.5%           |

*Note: OL = observational study; DB = double-blind study; NS = not significant.*
### Systematic review of paliperidone in the Chinese population

Ma et al. NR Paliperidone ER 7.6 3–12 80 8 −28.5*** (55.4) NS 68.75%

Cao et al. NR Paliperidone ER 7.6 3–12 30 12 −45.0** (53.9) NS 93.3%

Su et al. NR Paliperidone ER 6.25 3–9 32 8 −38.60 (58.95) NS 78.13%

Liang Olanzapine 10 5–10 34 0.05 97.37%

Guo et al. NR Paliperidone ER 6.5 3–12 30 8 −40.8*** (49.76) <0.05 79.6%

Zhang et al. DB Paliperidone ER 5–15 145 0.0001 Patients had received 14 days of treatment before attaining baseline PANSS scores

### Aripiprazole

Zhang et al. OL Paliperidone ER 6.4 3–12 81 52 −32.2*** (36.96) <0.05

Aripiprazole 14.5 90 −21.2** (23.61)

Ziprasidone 65.3 83 −18.7** (21.25)

Xie et al. NR Paliperidone ER 9 3–12 34 12 −38.6** (42.97) NS 72%

Aripiprazole 15 2.5–20 34 −35.5** (40.62) 68%

Zhou et al. NR Paliperidone ER 3–12 38 8 −60.0* (57.58) NS 86.8%

Aripiprazole 5–20 40 −58.4* (56.43) 85%

### Clozapine

Luo et al. NR Paliperidone ER 7.6 3–12 30 12 −49.4** (52.83) NS

Clozapine 278.7 200–500 30 −44.6** (48.38)

Liu et al. OL Paliperidone ER 6.12 3–9 25 12 −32.8** (39.01) NS 72%

Clozapine 498.00 25–600 25 −31.96** (37.56) 68%

### Ziprasidone

Zhang et al. OL Paliperidone ER 6.4 3–12 81 52 −32.2** (36.96) <0.05

Aripiprazole 14.5 90 −21.2** (23.61)

Ziprasidone 65.3 83 −18.7** (21.25)

He et al. DB Paliperidone ER 6.2 3–12 70 8 −49.24** (49.48) <0.05 90%

Ziprasidone 80.8 40–160 70 −44.13** (44.72) 74.3%

### Placebo

Rui et al. DB Paliperidone ER 9.5 3–12 64 56 1.69 (32.82) <0.0001

Placebo 71 2 (3.75)

### Others

Liu et al. NR Paliperidone ER + magnesium valproate 6–9 23 12 −56.7* (53.69) <0.05

Paliperidone ER 250–900 23 −37.3* (35.62)

(Continued)
## Table 1 (Continued)

| References | Blind | Treatment arms | Dose (mg/d) | Number of patients (enrolled) | Duration (weeks) | Mean change (% reduction versus baseline) | P-value | Response rate (%) | Remarks |
|------------|-------|----------------|-------------|-------------------------------|-----------------|-------------------------------------------|---------|-------------------|---------|
|            |       |                | Recall      |                               |                 |                                            |         |                   |         |
| Liu et al  | NR    | Paliperidone ER| 3–12        | 58                            | 24              | **−51.47** (60.61)                         | <0.05   |                   |         |
|            |       | Typical antipsychotics |         |                               |                 | **−43.27** (50.79)                         |         |                   |         |
|            |       | Atypical antipsychotics |         |                               |                 | **−48.62** (57.42)                         |         |                   |         |
| Liang et al| DB    | Paliperidone ER + aripiprazole | 6.0  | 20                            | 4               | **−12.9** (17.74)                          | <0.05   |                   |         |
|            |       | Paliperidone ER | 9.6        | 21                            |                 | **−28.9** (36.44)                          |         |                   |         |
| Yan et al  | NR    | Paliperidone ER + escitalopram | 6.2  | 42                            | 12              | **−16.13** (22.13)                         | <0.05   | 85.7%             |         |
| Luo et al  | NR    | Paliperidone ER | 6.5        | 42                            |                 | **−12.11** (16.49)                         | 64.3%   |                   |         |
|            |       | 3 mg paliperidone ER | 3  | 20                            | 8               | **−23.41** (26.42)                         | <0.05   | 70%               |         |
|            |       | 6 mg paliperidone ER | 6  | 20                            |                 | **−30.58** (34.34)                         | 80%     |                   |         |
|            |       | 9 mg paliperidone ER | 9  | 20                            |                 | **−36.54** (41.07)                         | 85%     |                   |         |
|            |       | 12 mg paliperidone ER | 12  | 20                            |                 | **−36.82** (41.66)                         | 85%     |                   |         |
| Paliperidone palmitate |     |                | Recall      |                               |                 |                                            |         |                   |         |
| Jiang et al| OL    | Paliperidone ER | 3–12        | 40                            | 13              | **−8.0** (15.15)                           | NS      |                   |         |
|            |       | Paliperidone palmitate | 75–150     | 40                            |                 | **−10.2** (18.92)                          |         |                   |         |

**Notes:** Response rate definition – A: response = PANSS reduction ≥ 25%; B: response = (PANSS in baseline − PANSS in visit point)/(PANSS in baseline − 30) 100% ≥ 50%; C: response = relief + improvement; D: response = (BPRS in baseline − BPRS in visit point)/(BPRS in baseline − 18) 100% ≥ 20%; E: response = PANSS reduction ≥ 20%; F: response = BPRS reduction ≥ 80%; G: response = PANSS reduction ≥ 50%; H: response = PANSS reduction ≥ 30%; I: response = (PANSS in baseline − PANSS in visit point)/(PANSS in baseline − 39) 100% ≥ 25%; J: response = not reported. *P < 0.05; **P < 0.01; ***P < 0.001.

**Abbreviations:** BPRS, Brief Psychiatric Rating Scale; DB, double-blind; ER, extended-release; NR, not reported; NS, not significant; OL, open-label; PANSS, Positive and Negative Syndrome Scale.
scores. The median change in PANSS total score was −38.60 in RCTs, and −34.48 in single-arm studies. In almost two-thirds of RCTs (21/33), the relative reduction in PANSS total score at the end point was >40%. Response rate was also a commonly used item to identify symptom outcome, but the definitions were different, and it was difficult to unify the definition of response.

Most of these studies were short-term studies, with duration of 4–12 weeks. Only three studies evaluated the long-term efficacy and safety of paliperidone ER: the duration of one study was 6 months, and that of the other two was 1 year.5-10 The results were consistent with other international data. Paliperidone ER was efficacious in the long term and significantly delayed relapse in Chinese patients with schizophrenia. No new safety signals were detected.

Onset of action
Consistent results reported that paliperidone ER has a much more rapid onset of action than risperidone or olanzapine in the first week (Table 2). Eight RCTs presented PANSS or Brief Psychiatric Rating Scale (BPRS) total score data in week 1; three of these compared the data for paliperidone ER with that for risperidone, and five compared the data for paliperidone ER with that for olanzapine. In all these eight studies, paliperidone ER effected significant reduction in PANSS total score at week 1 compared with that at baseline. The paliperidone ER group achieved lower PANSS or BPRS total score at week 1 in all studies compared with risperidone (3/3, P<0.05), and in most studies compared with olanzapine (3/5, P<0.05). Paliperidone ER treatment also resulted in significantly lower PANSS or BPRS total scores compared with risperidone in week 2; however, the results were comparable with those for olanzapine. There was not enough information to determine the dose details in week 1 and week 2, but the OROS® technology of paliperidone ER allowed initiation with effective dosage, which could benefit the onset.

Effectiveness outcomes
Seventeen comparative studies and 12 single-arm studies reported effectiveness outcomes, including functionality, neurocognitive function, and quality of life. The most commonly used effectiveness assessment was the Personal and Social Performance Scale (PSP) to assess functionality. Eleven comparative studies and ten single-arm studies reported PSP outcome. Paliperidone ER treatment significantly improved the PSP score at the end point compared with that at baseline in all these studies (Table 3). In all eleven comparative studies, paliperidone ER resulted in significantly better PSP scores at the end point than those achieved with comparative drugs, including risperidone, olanzapine, and aripiprazole.

Three comparative studies and three single-arm studies reported neurocognitive function outcome,11-16 assessed by different tools including the Wisconsin Card Sorting Test, Wechsler Memory Scale-Revised, Stroop, or Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative – Consensus Cognitive Battery. Neurocognitive outcome was the primary outcome in one comparative study and three single-arm studies. In all these studies, paliperidone ER treatment significantly improved neurocognitive function at the end point compared with that at baseline.

Quality of life was assessed in four trials,12,17-19 using different tools including the Short Form-36 Health Survey, The World Health Organization Quality of Life 100, Social Disability Screening Schedule, and Overall Quality of Life Rating Scale. In all these studies, paliperidone ER treatment significantly improved the quality of life at the end point compared with that at baseline.

Safety and tolerability
Safety and tolerability outcome was reported in most studies. The most commonly reported treatment-emergent adverse events (TEAEs) were extrapyramidal symptoms (EPSs), insomnia or somnolence, and prolactin-related TEAEs. Paliperidone ER was generally well tolerated in the Chinese population, and no special safety signal was found.

Extrapyramidal symptoms
EPSs were the most frequently reported TEAE reported in these articles as EPS, akathisia, dyskinesia, tumor, dystonia, and Parkinsonism. The incidence of EPSs associated with paliperidone ER treatment was lower than that with risperidone treatment but higher than that with olanzapine treatment.

Prolactin elevation
Six RCTs and three single-arm studies tested plasma prolactin level; the study duration ranged from 4 to 12 weeks. Paliperidone ER significantly increased plasma prolactin level compared with that at baseline. The prolactin level in the paliperidone ER group was significantly lower than that in the risperidone group but higher than that in the olanzapine and aripiprazole groups. The potential prolactin-related TEAEs were not especially reported in most studies. In five studies that reported potential prolactin-related TEAEs, including irregular menstruation, amenorrhea, galactorrhea, and gynecomastia, the total incidence was 0%–5%.17,20-23
### Table 2 PANSS total score in week 1–2 in RCTs

| References       | Treatment arms | PANSS total score | Dose titration                                                                 | Remarks                                                                 |
|------------------|----------------|-------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Li et al<sup>17</sup> | Paliperidone ER | Baseline          | 95.4                                                             | 88.0<sup>**</sup>                                                            | 83.3<sup>**</sup>                                                            | 6 mg/d was recommended; 9–12 mg/d was used when necessary |
|                  | Risperidone    | Week 1            | 97.2                                                             | 92.9                                                                     | 88.3                                                                  | 2 mg/d was recommended; 4–6 mg/d was used when necessary |
| Na et al<sup>20</sup> | Paliperidone ER | Week 2            | 84.0                                                             | 65.1<sup>**</sup>                                                            | 6 mg/d                                                                |                                                                                                           |
|                  | Risperidone    |                   | 84.5                                                             | 79.0                                                                    |                                                                                                                                   |
| Li et al<sup>29</sup> | Paliperidone ER |                   | 87.00                                                           | 69.43<sup>***</sup>                                                          | 58.78<sup>***</sup>                                                          | Started with 3 mg/d; 9–12 mg/d was used when necessary. The average dose was 8.32 mg/d |
|                  | Risperidone    |                   | 86.55                                                           | 81.70                                                                   | 60.20<sup>**</sup>                                                          | Started with 1 mg/d; 4–6 mg/d was used when necessary. The average dose was 5.86 mg/d |
| Zhang et al<sup>30</sup> | Paliperidone ER |                   | 81.5                                                             | 64.7<sup>**</sup>                                                            |                                                                                                                                   |
|                  | Risperidone    |                   | 80.8                                                             | 75.1<sup>**</sup>                                                            |                                                                                                                                   |
| Yuan et al<sup>31</sup> | Paliperidone ER |                   | 93.49                                                           | 80.51<sup>**</sup>                                                          | 68.84<sup>**</sup>                                                          | Started with 3 mg/d; increased to 6–12 mg/d in 2 weeks according to clinical judgment. The average dose was 8.9 mg/d |
|                  | Risperidone    |                   | 94.86                                                           | 86.50<sup>**</sup>                                                          | 75.86<sup>**</sup>                                                          |                                                                                                           |
| Li et al<sup>32</sup> | Paliperidone ER |                   | 86.32                                                           | 67.02<sup>**</sup>                                                          |                                                                                                                                   |
|                  | Risperidone    |                   | 85.96                                                           | 73.04<sup>**</sup>                                                          |                                                                                                                                   |
| Liu et al<sup>34</sup> | Paliperidone ER |                   | 81.68                                                           | 57.91<sup>**</sup>                                                          |                                                                                                                                   |
|                  | Risperidone    |                   | 80.82                                                           | 65.41<sup>**</sup>                                                          |                                                                                                                                   |
| Zhu et al<sup>34</sup>  | Paliperidone ER |                   | 89.16                                                           | 82.58<sup>**</sup>                                                          | 76.79<sup>**</sup>                                                          | Started with 3 mg/d; increased to 6–12 mg/d (average 9.5) in 1 week |
|                  | Olanzapine     |                   | 89.23                                                           | 83.69                                                                   | 80.62<sup>**</sup>                                                          | Started with 5 mg/d; increased to 10–20 mg/d (average 14.6) in 1 week |
| Xie et al<sup>36</sup>  | Paliperidone ER |                   | 88.82                                                           | 80.4                                                                   | 68.33<sup>**</sup>                                                          | Started with 3 mg/d; another 3 mg/d was added every 1–2 weeks; final dose ranged from 3 to 12 mg/d according to clinical judgment. The average dose was 6.4 mg/d |
|                  | Olanzapine     |                   | 86.39                                                           | 76.83<sup>**</sup>                                                          |                                                                                                                                   |
| Ma et al<sup>37</sup>   | Paliperidone ER |                   | 51.4                                                            | 43.8<sup>**</sup>                                                            | 39.7<sup>**</sup>                                                            | Started with 3 mg/d; increased to 6–12 mg/d after 1 week. The average dose was 7.6 mg/d BPRS |
|                  | Olanzapine     |                   | 50.6                                                            | 48.2                                                                    | 40.4<sup>**</sup>                                                            | Started with 10 mg/d; increased to 15–20 mg/d after 1 week. The average dose was 17.8 mg/d |
| Cao et al<sup>38</sup>   | Paliperidone ER |                   | 85.4                                                            | 77.1<sup>**</sup>                                                            | 73.8<sup>**</sup>                                                            | Started with 3 mg/d; adjusted to 3–12 mg/d in 2 weeks according to clinical judgment |
|                  | Olanzapine     |                   | 82.2                                                            | 80.4                                                                    | 75.5                                                                  | Started with 5 mg/d; adjusted to 5–20 mg/d in 2 weeks according to clinical judgment |
| Su et al<sup>39</sup>   | Paliperidone ER |                   | 65.48                                                           | 54.80<sup>**</sup>                                                          | 40.10<sup>**</sup>                                                          | Started with 6 mg/d; adjusted to 3–9 mg/d in 1–2 weeks according to clinical judgment. The average dose was 6.25 mg/d |
|                  | Olanzapine     |                   | 66.26                                                           | 61.35<sup>**</sup>                                                          | 40.74                                                                  |                                                                                                           |
| Liang et al<sup>40</sup> | Paliperidone ER |                   | 97.08                                                           | 67.97<sup>**</sup>                                                          | 55.29                                                                  | Started with 3 mg/d or 6 mg/d for severe cases; increased to 6 or 12 mg/d in 10 days |
|                  | Olanzapine     |                   | 96.55                                                           | 73.11<sup>**</sup>                                                          | 58.45                                                                  | Started with 5 mg/d or 10 mg/d for severe cases; increased to 15 or 20 mg/d in 10 days |
| Guo et al<sup>41</sup>  | Paliperidone ER |                   | 82                                                              | 55.8                                                                   |                                                                                                                                   |
|                  | Olanzapine     |                   | 76.6                                                            | 63.8                                                                    |                                                                                                                                   |

**Notes:** Versus baseline: *P* < 0.05; **P** < 0.01; ***P** < 0.001. Versus comparison group: *P* < 0.05; **P** < 0.01.

**Abbreviations:** BPRS, Brief Psychiatric Rating Scale; ER, extended-release; PANSS, Positive and Negative Syndrome Scale; RCTs, randomized controlled trials.
Table 3 PSP score of paliperidone ER studies

| References | Study design | Treatment arms | PSP score | Remarks |
|------------|--------------|----------------|-----------|---------|
|            |              |                | Baseline | Week 1 | Week 2 | Week 4 | Week 6 | Week 8 | Week 12 | Week 24 | |
| Li et al17 | RCT          | Paliperidone ER | 46.8     | 47.9   | 54.6*  | 60.3*  |         |         |         |         |         |
|            |              | Risperidone     | 47.2     | 48.1   | 52.7*  |         |         |         |         |         |
| Su et al46 | RCT          | Paliperidone ER | 45.57    |         | 64.46* | 74.32* |         |         |         |         |         |
|            |              | Risperidone     | 44.12    |         | 63.32* | 59.87* |         |         |         |         |         |
| Ren et al57| RCT          | Paliperidone ER | 31.77    | 48.72* | 37.67  |         |         |         |         |         |         |
|            |              | Risperidone     | 32.54    |         |         |         |         |         |         |         |         |
| Zhou et al48| RCT        | Paliperidone ER | 27.98    |         |         |         |         |         |         |         |         |
|            |              | Risperidone     | 28.52    |         |         |         |         |         |         |         |         |
| Li et al59 | RCT          | Paliperidone ER | 56.87    |         | 69.78* | 78.59* |         |         |         |         |         |
|            |              | Risperidone     | 57.35    |         | 61.38  | 66.57* |         |         |         |         |         |
| Yuan et al60| RCT         | Paliperidone ER | 32.79    | 38.12** | 51.67**| 59.79**| 65.74**|         |         |         |         |
|            |              | Risperidone     | 31.55    | 35.24**| 45.05**| 53.29**| 60.10**|         |         |         |         |
| Xie et al61| RCT          | Paliperidone ER | 32.75    |         |         |         |         | 51.58**| 68.85**|         |         |
|            |              | Risperidone     | 31.47    |         |         |         |         |        | 60.13**|         |         |
| Liang et al62| RCT        | Paliperidone ER | 25.00    | 41.79* | 52.37* | 68.74**| 77.11**|         |         |         |         |
|            |              | Olanzapine      | 27.06    | 40.26* | 51.05* | 62.53* | 70.05* |         |         |         |         |
| Xie et al63| RCT          | Paliperidone ER | 32.75    |         |         |         |         | 52.68**| 69.87**|         |         |
|            |              | Aripiprazole    | 32.47    |         |         |         |         | 46.05**| 61.24**|         |         |
| Zhou et al64| RCT         | Paliperidone ER | 45.2     |         |         |         |         | 78.0** |         |         |         |
|            |              | Aripiprazole    | 46.5     |         |         |         |         | 55.1   |         |         |         |
| Liu et al65| RCT          | Paliperidone ER | 50.72    |         | 66.91**|         |         | 71.89**| 78.87**|         |         |
|            |              | Typical antipsychotics | 51.57 | 58.25** | 52.68** | 52.00** |         |         |         |         |         |
|            |              | Atypical antipsychotics | 50.51 | 58.32** | 68.30** | 70.89** |         |         |         |         |         |
| Huang et al66| Single arm  | Paliperidone ER | 47.07    |         |         |         |         | 56.61**|         |         |         |
| Shi et al48| Single arm   | Paliperidone ER | 54.3     |         |         |         |         | 73.4** |         |         |         |
| Si et al69 | Single arm   | Paliperidone ER | 41.4     |         | 66.9   | 75.5** |         |         |         |         |         |
| Yang et al70| Single arm  | Paliperidone ER | 47.0     |         |         |         |         |         |         |         |         |
| Wang et al71| Single arm  | Paliperidone ER | 52.28    |         | 64.44**| 70.36**|         |         |         |         |         |
| Zhou et al72| Single arm  | Paliperidone ER | 39.5     | 52.5** | 62.6** | 70.5** |         |         |         |         |         |
| Sun et al73| Single arm   | Paliperidone ER | 33.57    |         |         |         |         |         |         |         |         |
| Wang et al74| Single arm  | Paliperidone ER | 51.26    | 61.13**| 61.17**| 69.43**|         |         |         |         |         |
| Zhang et al75| Single arm  | Paliperidone ER | 58.6     |         |         |         |         |         |         |         |         |

**Notes:** Versus baseline: *P<0.05; **P<0.01. Versus comparison group: +P<0.05; ++P<0.01. 
**Abbreviations:** ER, extended-release; PSP, Personal and Social Performance Scale; RCT, randomized controlled trial.
Weight and metabolic parameters
Eight RCTs and four single-arm studies reported outcomes related to weight gain and metabolic parameters. Most of the studies had a duration of 6–12 weeks, except a 52-week study. The most commonly assessed metabolic parameters were levels of glucose and lipids in plasma. In the 6- to 12-week studies, paliperidone ER treatment resulted in an insignificant change or significant but mild change in mean weight. Paliperidone ER treatment caused no significant change in blood glucose levels. In most studies, paliperidone ER treatment caused no significant change in lipid metabolism, although some studies showed a small increase in triglyceride levels. Generally, in these short-duration studies, paliperidone ER was well tolerated in terms of effect on weight and metabolic parameters, and had some advantage over olanzapine in terms of weight gain, and glucose and lipid metabolism.21,22,24

Paliperidone palmitate
PP-related studies in the Chinese population included two pharmacokinetic studies, four comparative studies, and three single-arm studies.

Among the pharmacokinetic studies, the first one was an open-label, randomized, parallel-group, multicenter study in patients with chronic schizophrenia.25 On day 1, 48 eligible subjects were randomly assigned in a 1:1:1 ratio to 25, 100, or 150 mg PP groups; the same dose as that assigned on day 1 was injected on day 8 on the other side of the gluteal muscle. The plasma concentrations of paliperidone gradually increased to a C_{max} at a mean t_{max} of 13 days. The area under the curve (AUC) (0–35 days), AUC (0–210 days), and AUC (0–∞) for the three doses were dose-proportional. The median half-life (t_{1/2}) ranged from 42 to 77 days, and the t_{1/2} was prolonged for higher doses. The therapeutic regimen for PP in this study was different from the recommended regimen. The second study was designed to evaluate the pharmacokinetics of PP after multiple doses (the recommended dosing regimen): 150 mg on day 1, followed by 100 mg on day 8.26 Thereafter, a flexible dose (75, 100, or 150 mg) was administered monthly, based on the patient’s response, consecutively for 6 months. The mean C_{max} was 17–25 ng/mL at a mean t_{max} of 11–17 days. Based on these data, the pharmacokinetic characteristics of PP in the Chinese population were similar to those found in studies on the Caucasian population.27,28

The first comparative study was a registration study to establish the effects of PP on acute or recent-onset patient hospitalization rates.33–35 The results showed that PP treatment significantly (P<0.0001) reduced both the number of hospitalizations and the number of days spent in the hospital. The most frequently reported TEAEs were injection-site pain, EPSs, akathisia, and insomnia.

Discussion
This study was a systematic review carried out to critically evaluate the efficacy, effectiveness, and safety of paliperidone (as the oral ER and 1-month long-acting injection formulations) in the Chinese population. The results demonstrated that the efficacy of paliperidone ER was at least comparable with that of other atypical antipsychotics, which was consistent with the results of the latest meta-analysis of Chinese patients with schizophrenia.36 The onset of symptom control was faster in the paliperidone ER group, compared with the risperidone group at week 1 and week 2, and the olanzapine treatment at week 1. This may be because the OROS® technology and pharmacokinetic profile of paliperidone ER allow once-daily dosing with an initial dose of 6 mg and no need for initial dose titration, which enables rapid action. A review summarized the time required to achieve significant alleviation of psychiatric symptoms compared with baseline:37 paliperidone ER and risperidone showed alleviation of symptoms from day 4, while olanzapine, aripiprazole, and ziprasidone took 1–2 weeks. However, there were no available head-to-head comparison results. Our findings could help to enrich the data on antipsychotic onset of action. Paliperidone was well tolerated in the Chinese population, and no special safety issues were found. The incidence of EPSs and increase in prolactin levels associated with paliperidone ER treatment were lower than that with risperidone treatment but higher than that with olanzapine treatment. This was consistent with the result of other studies.

Paliperidone ER treatment resulted in a significantly better PSP score at the end point compared with other antipsychotics.
including risperidone, olanzapine, and aripiprazole. This was a novel finding of our systematic review. There are a limited number of randomized controlled studies comparing paliperidone ER and other antipsychotics in international publications. No RCTs have compared the functionality outcome between paliperidone ER and risperidone or aripiprazole. Three 6-week studies identified the efficacy and safety of paliperidone ER, and used olanzapine 10 mg/d treatment to confirm trial validity; the pooled data showed that there was no significant difference in mean PSP score change from baseline to end point between paliperidone ER and olanzapine groups. A period of 6 weeks may not be enough to test the functionality outcome, as it is influenced by several factors, including not only positive symptoms but also negative symptoms, affective symptoms, cognitive symptoms, and side effects such as sedation and metabolic syndrome.\(^{38-42}\) The efficacy of paliperidone ER is at least comparable to that of other antipsychotics, and it has a better safety profile than risperidone, and less severe sedative and metabolic effects than olanzapine. This might be the reason for the better functionality outcome of paliperidone ER treatment found in our review. However, the sample size of studies included in this systematic review is relatively small, and PSP is not the primary end point in most studies, so the effectiveness of antipsychotics in functionality improvement still needs further verification in the future. Results from studies on PP demonstrated that it is an effective and well-tolerated treatment for Chinese patients with schizophrenia, and may have some advantage in terms of functionality and patient’s medication satisfaction compared with the oral formulation. Additionally, several studies have demonstrated that LAI has an advantage over oral antipsychotics in preventing relapse, and in reducing hospitalization rate and number of hospitalization days.\(^ {34,43,44}\) The studies on PP were fewer than those on paliperidone ER; a People’s Republic of China international survey in 2012 showed that only 2.75% of patients with schizophrenia use LAI antipsychotics, and only 0.48% use atypical LAIs.\(^ {45}\) Both LAI data on clinical research and LAI usage in clinical practice need to be improved in the People’s Republic of China.

There were some problems related to study quality, especially with publications from Chinese core journals. Most of the RCTs from Chinese core journals in this review did not clearly elucidate the methods of randomization, or information about blinding. Some studies did not give detailed information about mean dose, which caused difficulty in comparing between different treatment arms. The duration of most studies was 6–12 weeks; long-term studies were relatively fewer. Additionally, the sample sizes of some studies were relatively small.

**Conclusion**

Paliperidone is one of the first-line antipsychotics used in the People’s Republic of China. Both paliperidone ER and PP are effective, safe, and well tolerated in Chinese patients with schizophrenia according to the data we reviewed. Paliperidone may have some advantage over other antipsychotics in terms of onset of action and functionality improvement. Future studies could focus more on long-term data and LAI treatment.

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**Author contributions**

All authors contributed toward data analysis, drafting and revising the paper, and agree to be accountable for all aspects of the work.

**Disclosure**

LiLi Zhang is an employee of Xian Janssen Medical Affairs. YanJie Zhao is an intern at Xian Janssen Medical Affairs. Xian Janssen did not provide any financial support for this work. The authors report no other conflicts of interest in this work.

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Table S1  Overview of study characteristics

| Study | Type | Study design | Blind | Primary sources of potential bias | Patient profile | Age overall or group means* | Sex (% male) | Outcome | Primary outcome measures | Available outcome measures |
|-------|------|--------------|-------|----------------------------------|-----------------|----------------------------|--------------|---------|--------------------------|------------------------------|
| Liu et al | CC | RCT | OL | Observer expectation | First-episode | 31.24, 32.04 | 54.0 | Efficacy, effectiveness | PANSS | PANSS, WCST, CPT, CT, WMS-R, PANSS, ERSR, SF36, PSP, metabolic measures, prolactin, adverse events |
| Li et al | CC | RCT | NR | Blinding, noncompleters excluded | | 20–59 | | Efficacy, effectiveness, safety | PANSS | PANSS, ERSR, SF36, PSP, metabolic measures, prolactin, adverse events |
| Su et al | CC | RCT | OL | Observer expectation | | 34.7, 35.4 | 48.9 | Efficacy, effectiveness, safety | PANSS, PSP | PANSS, PSP, MSQ, adverse events |
| Ren et al | CC | RCT | NR | Blinding | | 30.4, 31.2 | 63.2 | Efficacy, effectiveness, safety | PANSS | PANSS, PSP, adverse events |
| Zhou et al | CC | RCT | NR | Blinding, noncompleters excluded | First-episode | 27.6, 26.9 | 47.2 | Efficacy, effectiveness, safety | PANSS | PANSS, prolactin, metabolic measures, TESS |
| Na et al | CC | RCT | OL | Observer expectation | | 33.7, 34.5 | 48.8 | Efficacy, safety | PANSS | PANSS, TESS, laboratory examination, PSP |
| Li et al | CC | RCT | NR | Blinding | Adolescent | 16.61 | 41.2 | Efficacy, effectiveness, safety | PANSS | PANSS, TESS |
| Zhang et al | CC | RCT | NR | Blinding, noncompleters excluded | | 32, 33 | 46.2 | Efficacy, safety | PANSS | PANSS, CGL, PSP |
| Yuan et al | CC | RCT | NR | Blinding, noncompleters excluded | | 33.1, 34.5 | 56.5 | Efficacy, effectiveness | PANSS | PANSS, CGL, PSP |
| Li et al | CC | RCT | OL | Observer expectation, noncompleters excluded | First-episode, male | 28.6, 27.9 | 100.0 | Efficacy, safety | PANSS, metabolic measures | PANSS, metabolic measures |
| Deng et al | CC | RCT | OL | Observer expectation | First-episode, female | 27.08, 26.00 | 0.0 | Efficacy, safety | BPRS | BPRS, TESS |
| Liu et al | CC | RCT | DB | | First-episode | 29, 30 | 53.3 | Efficacy, safety | PANSS | PANSS, TESS, metabolic measures, prolactin |
| Wang et al | CC | RCT | OL | Observer expectation | | 35, 37 | 45.7 | Efficacy, effectiveness, safety | PANSS | PANSS, SDSS, TESS |
| Hu et al | Int | RCT | OL | Observer expectation, noncompleters excluded | First-episode, male | 25.24, 28.65 | 69.1 | Efficacy, safety | PANSS, metabolic measures | PANSS, metabolic measures, adverse events, prolactin |
| Zhu et al | CC | RCT | NR | Blinding | Refractory | 42.7, 43.5 | | Efficacy, safety | PANSS | PANSS, TESS, metabolic measures |
| Xie et al | CC | RCT | OL | Observer expectation, noncompleters excluded | First-episode, adolescent | 13.5, 14.6 | 50.7 | Efficacy, effectiveness, safety | PANSS | PANSS, PSP, TESS, laboratory examination |
| Ma et al | CC | RCT | NR | Blinding | | 38.6, 39.4 | 53.2 | Efficacy, safety | BPRS | BPRS, TESS |
| Study | Design | Treatment | Blinding | First-episode | Efficacy, safety | PANSS, metabolic measures | Other outcomes |
|-------|--------|-----------|----------|--------------|----------------|----------------------------|---------------|
| Cao et al | CC RCT | NR | Blinding | 26.00, 27.12 | 53.2 | Efficacy, safety | PANSS, TESS |
| Su et al | CC RCT | NR | Blinding | 31.0, 32.0 | 51.5 | Efficacy, safety | BPRS, SAPS, TESS |
| Liang | CC RCT | OL | Observer expectation, noncompleters excluded | 30.42, 29.47 | 53.9 | Efficacy, effectivenes, safety | PANSS, PSS, TESS |
| Guo et al | CC RCT | NR | Blinding | 35.8, 33.6 | 68.3 | Efficacy, safety | Liver function, PANSS, TESS |
| Zhang et al | CC RCT | DB | Blinding | 33, 34 | 54.2 | Efficacy, safety | PANSS, CGI-S, adverse events, metabolic measures, VAS, AIMS, BARS, SAS, prolactin |
| Paliperidone ER compared with aripiprazole | Zhang et al | Int RCT | OL | Observer expectation, noncompleters excluded | 27.1, 25.7, 26.3 | 38.9 | Efficacy, safety | PANSS, metabolic measures, PANSS, CGI-S, metabolic measures |
| Xie et al | CC RCT | NR | Blinding, noncompleters excluded | 14, 15 | 52.4 | Efficacy, effectiveness, safety | PANSS, PSS, TESS |
| Zhou et al | CC RCT | NR | Blinding | 35.8, 35.5 | 100.0 | Efficacy, effectiveness, safety | PANSS, PSS, sexual function, prolactin |
| Paliperidone ER compared with clozapine | Luo et al | CC RCT | NR | Blinding | 33.4, 32.9 | 51.7 | Efficacy, effectiveness, safety | PANSS, TESS, WHOQOL-100, SDSS, WMS-R, PANSS, TESS |
| Liu et al | CC RCT | OL | Observer expectation | Refractory | 41.46, 39.84 | 58.0 | Efficacy, safety | PANSS, TESS |
| Zhang et al | Int RCT | OL | Observer expectation, noncompleters excluded | First-episode | 27.1, 25.7, 26.3 | 38.9 | Efficacy, safety | PANSS, CGI-S, metabolic measures, PANSS, TESS |
| He et al | CC RCT | DB | Noncompleters excluded | 33.4, 32.8 | 52.9 | Efficacy, effectiveness, safety | GQOLI-74, PANSS, TESS |
| Paliperidone ER compared with placebo | Rui et al | Int RCT | DB | 31.1, 32.3 | 40.7 | Efficacy, efficacy, safety | Relapse, PANSS, CGI-S, TEAes |
| Paliperidone ER compared with others | | | | | | | |
| Paliperidone ER compared with paliperidone ER + magnesium valproate | Liu et al | CC RCT | NR | Blinding | 36.0 | 76.1 | Efficacy, safety | PANSS, TESS |
| Paliperidone ER compared with typical antipsychotics and atypical antipsychotics | Liu et al | CC RCT | NR | Blinding, noncompleters excluded, concomitant antipsychotics | 33.91, 33.77, 34.04 | 52.0 | Efficacy, effectiveness, safety | PANSS, PSS, TESS |
| Paliperidone ER compared with paliperidone ER + aripiprazole | Liang et al | CC RCT | DB | Noncompleters excluded | 30.8, 30.3 | 37.5 | Efficacy, safety | PANSS, AIMS, BARNES, UKU, prolactin |

(Continued)
| Study design | Study design | Primary sources of potential bias | Patient profile | Age overall or group means* | Sex (% male) | Outcome | Primary outcome measures | Available outcome measures |
|--------------|--------------|----------------------------------|----------------|----------------------------|-------------|---------|-------------------------|---------------------------|
| Paliperidone ER compared with paliperidone ER + escitalopram | CC | RCT | NR | Blinding | 39.6, 38.4 | 51.2 | Efficacy, effectiveness, safety | WAIS, WCST, TESS |
| Different dose groups of paliperidone ER | CC | RCT | NR | Blinding | 18–62 | 52.5 | Efficacy, safety | PANSS |
| Luo et al** | Int | Single-arm study | OL | Observer expectation | 40.3 | 54.6 | Efficacy, effectiveness, safety | PANSS |
| Tsai et al** | Int | Single-arm study | NR | Blinding | NR | NR | Effectiveness | DAI-10 |
| Shi et al** | Int | Single-arm study | OL | Observer expectation | 27.6 | 48.9 | Efficacy, effectiveness, safety | PSP, MATRICS |
| Si et al** | Int | Single-arm study | OL | Observer expectation, noncompleters excluded | First-episode | 30.0 | 50.0 | Efficacy, effectiveness, safety | PSP |
| Tang** | Int | Single-arm study | OL | Observer expectation | 40.1 | 46.1 | Efficacy, effectiveness | PANSS, PSP |
| Wang et al** | CC | Single-arm study | NR | Blinding, noncompleters excluded | 18–40 | 69.2 | Efficacy, effectiveness, safety | PANSS |
| Li et al** | CC | Single-arm study | NR | Blinding, concomitant antipsychotic | Adolescent | 14.4 | 43.6 | Efficacy, safety | PANSS |
| Wu et al** | CC | Single-arm study | OL | Observer expectation, noncompleters excluded | 36.65 | 35.4 | Efficacy, safety | PANSS, metabolic measures |
| Zhou et al** | CC | Single-arm study | NR | Blinding | 28.7 | 47.2 | Efficacy, effectiveness, safety | PANSS |
| Chen et al** | CC | Single-arm study | OL | Observer expectation | 29.9 | 49.0 | Effectiveness | HVLT |
| Sun et al** | CC | Single-arm study | NR | Blinding, noncompleters excluded | First-episode, adolescent | 13.5 | 54.1 | Efficacy, effectiveness, safety | PANSS |
| Zhang et al** | CC | Single-arm study | NR | Blinding, noncompleters excluded | 35.89 | 45.2 | Effectiveness | WCST |
| Lv et al** | CC | Single-arm study | OL | Observer expectation, noncompleters excluded | 39.03 | 46.7 | Efficacy, safety | Metabolic measures |
| Wang et al** | CC | Single-arm study | NR | Blinding | 22.87 | 43.5 | Efficacy, effectiveness, safety | PANSS, prolactin |
| Study                      | Journal Type | Study Design          | Blinding | Age (years) | Sample Characteristics | Efficacy, Effectiveness, Safety | Abbreviations                                      |
|---------------------------|--------------|-----------------------|----------|-------------|------------------------|--------------------------------|---------------------------------------------------|
| Zhang et al23             | CC           | Single-arm study      | OL       | 31          | 49.5                   | Efficacy, effectiveness, safety | PANSS, CGI-S, PSP, ERSRS, metabolic measures, prolactin |
| Liu et al21               | CC           | Single-arm study      | NR       | 40          | 53.8                   | Efficacy                         | PANSS                                             |
| Xiong et al25             | CC           | Observational study   | NR       | 28.6, 29.2  | 58.7                   | Efficacy, safety                 | PANSS, TESS                                      |
| Si et al22                | Int          | Pharmacokinetic study | NR       | 19–35       | 54.2                   | Pharmacokinetics, safety, tolerability | Pharmacokinetics                                 |
| Paliperidone ER           |              |                       |          |             |                        |                                  |                                                   |
| Jiang et al20             | CC           | RCT                   | NR       | 32.7, 34.1  | 53.6                   | Efficacy, effectiveness, safety  | PANSS, TESS, PSP, MSQ                          |
| Paliperidone palmitate    |              |                       |          |             |                        |                                  |                                                   |
| Li et al20                | Int          | RCT                   | OL       | 31.5, 32.0  | 32.8                   | Efficacy, effectiveness, safety  | PANSS, PSP, CGI-S                              |
| Ma et al21                | CC           | RCT                   | OL       | 16.05, 15.57| 51.0                   | Efficacy, effectiveness, safety  | PANSS                                            |
| Yi et al22                | CC           | RCT                   | OL       | 31.5, 35.5  | 42.6                   | Efficacy, safety                 | PANSS                                            |
| Wakamatsu et al20         | Int          | RCT                   | DB       | 45          |                        | Efficacy, safety                 | PANSS, CGI-S, TEAEs                           |
| Zhang et al24             | Int          | Single-arm study      | OL       | 28.7        | 65.5                   | Efficacy, effectiveness, safety  | PANSS, CGI-SCH, MSQ, hospitalization              |
| Miao et al25              | CC           | Single-arm study      | OL       | 33.2        | 39.7                   | Efficacy, safety                 | PANSS, TESS                                      |
| Bressington et al21       | Int          | Retrospective observational study | | 40.86       | 71.2                   | Effectiveness                    | Hospitalization rate                          |
| Si et al23                | Int          | Pharmacokinetic study | OL       | 53          | 76.6                   | Pharmacokinetics, efficacy       | Pharmacokinetics                                 |
| Li et al24                | CC           | Pharmacokinetic study | NR       | 25.44       | 44.4                   | Pharmacokinetics, efficacy, safety | Pharmacokinetics                                 |

Note: Where two ages appear in this column, they indicate ages for the experimental group and for the comparison group, respectively.

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BARS/BARNeS, the Barnes Akathisia Rating Scale-revised; BPRS, Brief Psychiatric Rating Scale; BVMT-R, Wisconsin Brief Visuospatial Memory Tests; CC, Chinese core (journal type); CGI, Clinical Global Impression; CGI-S, Clinical Global Impression-Schizophrenia; CPT, Continuous Performance Task; CT, Number Cancellation Test; DAI-10, The Drug Attitude Inventory; DB, double-blind; eR, extended-release; ERSRS, Extrapyramidal Syndrome Rating Scale; GQOLi-74, The Overall Quality of Life Rating Scale; HVLT, Hopkins Verbal Learning Test-Revised; Int, international (journal type); MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; MSQ, Medication Satisfaction Questionnaire; NR, not reported; OL, open-label; PANSS, Positive and Negative Symptom Scale; PASAT, Paced Auditory Serial Addition Task; PSP, Personal and Social Functioning Scale; RCT, randomized controlled trial; SANS, Simpson Angus Scale; SDSS, Social Disability Screening Schedule; SF36, Short Form-36; Stroop, Stroop Color and Word Test; TEAEs, treatment-emergent adverse events; TESS, Treatment-Emergent Symptom Scale; TOH, tower of Hanoi; UKU, Udvalg for Kliniske Undersøgelser Side Effect Rating Scale; VAS, Visual Analog Scale; WAIS, Wechsler Adult Intelligence Scale; WAIS-III, Symbol Search Test; WCST, Wisconsin Card Sorting Test; WHOQOL, World Health Organization Quality of Life; WMS-R, Wechsler Memory Scale-Revised; WMS-III, Spatial Span subtest of Wechsler Memory Scale-III.
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