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REVIEW

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

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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 (D_2) receptors and 5-hydroxytryptamine 2A (5-HT_{2A}) receptors, with a higher affinity for 5-HT_{2A} receptors

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than for D_2 receptors. In addition, paliperidone also acts as an antagonist at α_1-adrenoceptors, and binds with lower affinity to α_2-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.[6] 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]

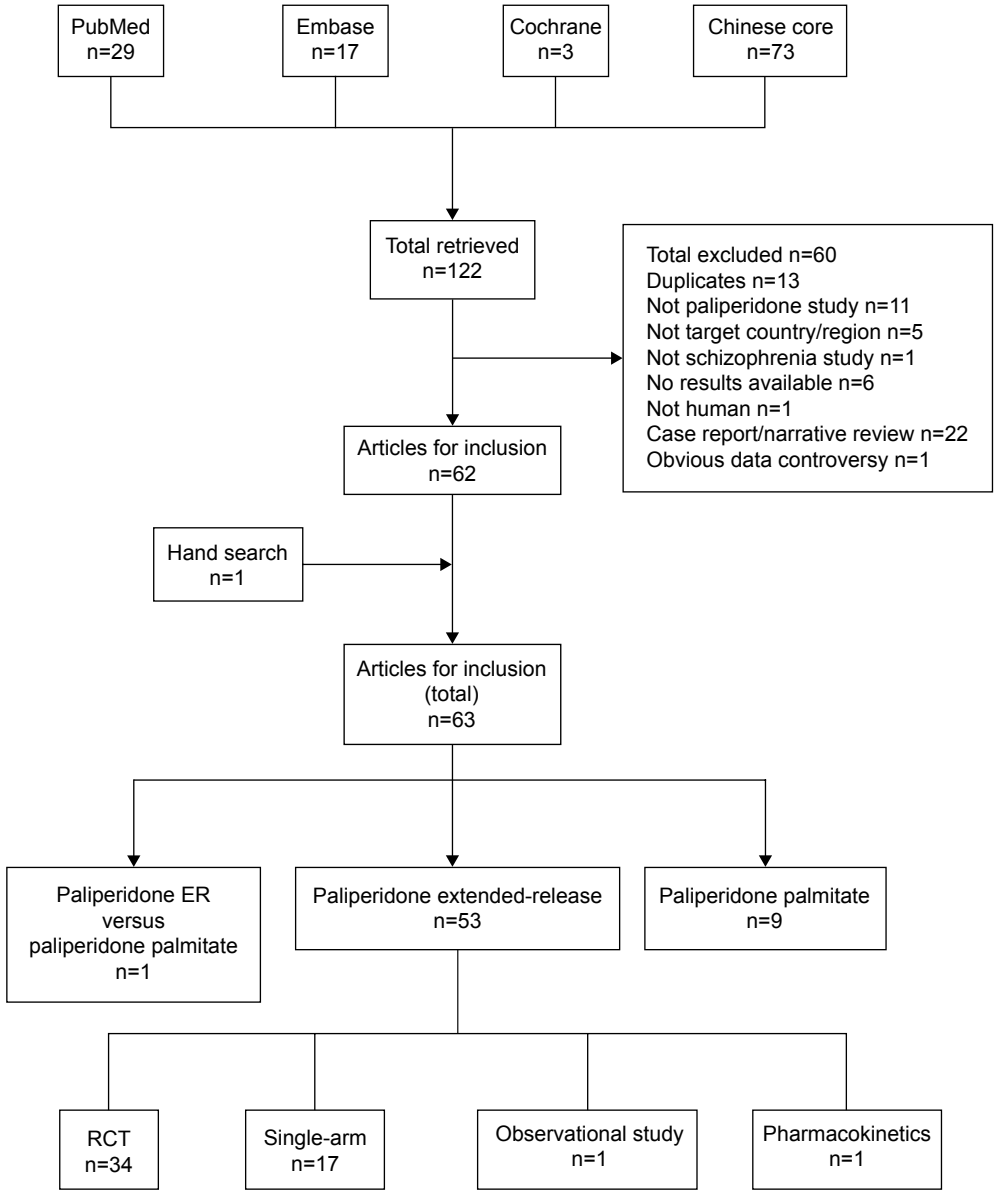

Figure 1 Flow diagram for study selection.
Abbreviations: ER, extended-release; RCT, randomized controlled trial.

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_{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

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
			Mean	Range			BPRS	PANSS			
Risperidone											
Liu et al[11]	OL	Paliperidone ER	6.60	3–9	25	8		–38.80** (42.23)	NS	80%[A]	
		Risperidone	4.40	1–6	25			–36.80** (40.51)		76%[A]	
Li et al[17]	NR	Paliperidone ER		6–12	48	12		–34.7* (36.37)	<0.05		
		Risperidone		2–6	62			–26.4* (27.16)			
Su et al[46]	OL	Paliperidone ER	6.3	3–12	47	12		–41.6* (48.54)	<0.05	64%[B]	
		Risperidone	3.8	1–6	45			–32.8* (38.41)		60%[B]	
Ren et al[47]	NR	Paliperidone ER		3–9	76	4		–48.73* (54.53)	<0.05		
		Risperidone		1–6	79			–39.15* (44.44)			
Zhou et al[48]	NR	Paliperidone ER		3–12	38	8		–59.77** (57.38)	NS	82.9%[A]	
		Risperidone		2–6	38			–43.23** (41.69)		86.5%[A]	
Na et al[20]	OL	Paliperidone ER		6	40	8		–39.7** (47.26)	NS	62.5%[B]	
		Risperidone		1–4	40			–41.3** (48.88)		67.5%[B]	
Li et al[49]	NR	Paliperidone ER	8.32	3–12	14	6		–37.86*** (43.52)	NS		
		Risperidone	5.86	1–6	20			–36.60*** (42.29)			
Zhang et al[50]	NR	Paliperidone ER	9	3–12	47	6		–28.2** (34.60)	NS	70%[B]	
		Risperidone	5	2–6	47			–27.4** (33.91)		66%[B]	
Yuan et al[51]	NR	Paliperidone ER	8.9	3–12	45	6		–38.42** (41.10)	NS		
		Risperidone	4.9	1–6	45			–37.46** (39.49)			
Li et al[52]	OL	Paliperidone ER	6.67	3–9	40	8		–38.37** (44.45)	NS	67.5%[C]	
		Risperidone	4.32	1–6	40			–36.88** (42.90)		65%[C]	
Deng et al[53]	OL	Paliperidone ER	8.76	6–12	38	6	–28.37 (57.52)		NS	94.74%[D]	
		Risperidone	5.42	4–8	38		–29.73 (58.48)			92.11%[D]	
Liu et al[54]	DB	Paliperidone ER	5.8		45	8		–44.26 (54.19)	<0.05		
		Risperidone	4.2		45			–41.47 (51.31)			
Wang et al[18]	OL	Paliperidone ER		3–12	41	12		–43.3** (46.31)	<0.05		
		Risperidone		1–8	40			–23.2 (25.27)			
Xiong et al[55]		Paliperidone ER	5.49	3–9	127	8		–28.4 (42.01)	<0.05	80.3%[E]	Observational study
		Risperidone		1–4	139			–24.0 (35.98)		74.8%[E]	
Olanzapine											
Hu et al[21]	OL	Paliperidone ER	7.55		40	12		–20.33*** (25.57)	NS		
		Olanzapine	15.87		40			–23.39*** (31.63)			
Zhu et al[24]	NR	Paliperidone ER	10.1	3–12	15	12		–30.87* (34.62)	NS	73%[A]	
		Olanzapine	14.6	5–20	15			–26.25* (29.42)		67%[A]	
Xie et al[56]	OL	Paliperidone ER	6.4	3–12	40	12		–35.60** (41.21)	NS	85.7%[A]	
		Olanzapine	17.5	2.5–20	40			–38.59** (43.45)		87.5%[A]	

Ma et al[57]	NR	Paliperidone ER	7.6	3–12	80	8	−28.5*** (55.4)		NS	68.75%[D]	
		Olanzapine	17.8	10–20	76		−28.9*** (57.1)			65.78%[D]	
Cao et al[58]	NR	Paliperidone ER		3–12	30	12		−45.0** (53.9)	NS	93.3%[A]	
		Olanzapine		5–20	32			−50.2** (58.7)		90.6%[A]	
Su et al[59]	NR	Paliperidone ER	6.25	3–9	32	8		−38.60 (58.95)	NS	78.13%[F]	
		Olanzapine	10	5–10	34			−39.12 (59.04)		76.47%[F]	
Liang[60]	OL	Paliperidone ER		3–12	39	6		−57.53* (59.26)	<0.05	97.37%[A]	
		Olanzapine		5–20	39			−53.26* (55.16)		78.95%[A]	
Guo et al[61]	NR	Paliperidone ER		3–12	30	8		−40.8** (49.76)	<0.05		
		Olanzapine		5–20	30			−31.4** (40.99)			
Zhang et al[22]	DB	Paliperidone ER		3–12	143	6		−32.3*** (38.8)	NS	71%[G]	
		Olanzapine		5–15	145			−34.1*** (39.8)		69.1%[G]	
Aripiprazole											
Zhang et al[9]	OL	Paliperidone ER	6.4		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[62]	NR	Paliperidone ER	9	3–12	34	12		−38.6** (42.97)	NS	72%[B]	
		Aripiprazole	15	2.5–20	34			−35.5** (40.62)		68%[B]	
Zhou et al[63]	NR	Paliperidone ER		3–12	38	8		−60.0* (57.58)	NS	86.8%[H]	
		Aripiprazole		5–20	40			−58.4* (56.43)		85%[H]	
Clozapine											
Luo et al[12]	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[64]	OL	Paliperidone ER	6.12	3–9	25	12		−32.88** (39.01)	NS	72%[I]	
		Clozapine	498.00	25–600	25			−31.96** (37.56)		68%[I]	
Ziprasidone											
Zhang et al[9]	OL	Paliperidone ER	6.4		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[19]	DB	Paliperidone ER	6.2	3–12	70	8		−49.24** (49.48)	<0.05	90%[A]	
		Ziprasidone	80.8	40–160	70			−44.13** (44.72)		74.3%[A]	
Placebo											
Rui et al[8]	DB	Paliperidone ER	9.5	3–12	64	56		16.9 (32.82)	<0.0001		Patients had received 14 days of treatment before attaining baseline PANSS scores
		Placebo			71			2 (3.75)			
Others											
Liu et al[65]	NR	Paliperidone ER + magnesium valproate		6–9 250–900	23	12		−56.7* (53.69)	<0.05		
		Paliperidone ER		6–9	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
			Mean	Range			BPRS	PANSS			
Liu et al[10]	NR	Paliperidone ER		3–12	58	24		–51.47** (60.61)	<0.05		
		Typical antipsychotics			57			–43.27** (50.79)			
		Atypical antipsychotics			60			–48.62** (57.42)			
Liang et al[66]	DB	Paliperidone ER + aripiprazole	6.0	3–12 10	20	4		–12.9 (17.74)	<0.05		
		Paliperidone ER	9.6	3–12	21			–28.9 (36.44)			
Yan et al[13]	NR	Paliperidone ER + escitalopram	6.2 15.2	3–9 10–20	42	12		–16.13* (22.13)	<0.05	85.7%[A]	
		Paliperidone ER	6.5	3–9	42			–12.11* (16.49)		64.3%[A]	
Luo et al[67]	NR	3 mg paliperidone ER	3	3	20	8		–23.41** (26.42)	<0.05	70%[J]	
		6 mg paliperidone ER	6	6	20			–30.58** (34.34)		80%[J]	
		9 mg paliperidone ER	9	9	20			–36.54** (41.07)		85%[J]	
		12 mg paliperidone ER	12	12	20			–36.82** (41.66)		85%[J]	
Paliperidone palmitate											
Jiang et al[68]	OL	Paliperidone ER		3–12	40	13		–8.0 (15.15)	NS		Patients had received 6 weeks of treatment before attaining baseline PANSS scores
		Paliperidone palmitate		75–150 (mg/month)	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%≥50%; 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 – 30)·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-third 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.[8–10] 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
		Baseline	Week 1	Week 2		
Li et al[17]	Paliperidone ER	95.4	88.0*,+	83.3*,+	6 mg/d was recommended; 9–12 mg/d was used when necessary	
	Risperidone	97.2	92.9	88.3*	2 mg/d was recommended; 4–6 mg/d was used when necessary	
Na et al[20]	Paliperidone ER	84.0		65.1**,+	6 mg/d	
	Risperidone	84.5		79.0*	Started with 1 mg/d; increased to 4 mg/d in 1 week	
Li et al[49]	Paliperidone ER	87.00	69.43***,+	58.78***	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***	Started with 1 mg/d; 4–6 mg/d was used when necessary. The average dose was 5.86 mg/d	
Zhang et al[50]	Paliperidone ER	81.5		64.7**,++	Started with 3 mg/d; an additional 3 mg/d was added every 1–2 weeks; final dose ranged from 3 to 12 mg/d. The average dose was 9 mg/d	
	Risperidone	80.8		75.1**	Started with 2 mg/d; an additional 2 mg/d was added every 1–3 days; dose was increased to 4–6 mg/d in 2 weeks. The average dose is 5 mg/d	
Yuan et al[51]	Paliperidone ER	93.49	80.51**,+	68.84**,+	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**	75.86**	Started with 1 mg/d; increased to 3–6 mg/d in 2 weeks according to clinical judgment. The average dose was 4.9 mg/d	
Li et al[52]	Paliperidone ER	86.32		67.02**,+	Started with 3 mg/d; increased to 6 mg/d in 1 week; a maximum of 9 mg/d was used according to clinical judgment. The average dose was 6.67 mg/d	
	Risperidone	85.96		73.04**	Started with 1 mg/d; increased to 4 mg/d in 1 week; a maximum of 6 mg was used according to clinical judgment. The average dose was 4.32 mg/d	
Liu et al[54]	Paliperidone ER	81.68		57.91***,+	Started with 6 mg/d; adjusted individual dose after 2 weeks according to clinical judgment. The average dose was 5.8 mg/d	
	Risperidone	80.82		65.41***	Started with 2 mg/d; adjusted individual dose in 2 weeks according to clinical judgment. The average dose was 4.2 mg/d	
Zhu et al[24]	Paliperidone ER	89.16	82.58+	76.79**	Started with 3 mg/d; increased to 6–12 mg/d (average 9.5) in 1 week	
	Olanzapine	89.23	83.69	80.62**	Started with 5 mg/d; increased to 10–20 mg/d (average 14.6) in 1 week	
Xie et al[56]	Paliperidone ER	88.82		68.33**,+	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**	Started with 2.5 mg/d; an additional 2.5–5 mg/d was added every 5–7 days; final dose ranged from 5 to 20 mg/d according to clinical judgment. The average dose was 17.5 mg/d	
Ma et al[57]	Paliperidone ER	51.4	43.8**,+	39.7**	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**	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[58]	Paliperidone ER	85.4	77.1*	73.8**	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[59]	Paliperidone ER	65.48	54.80*,+	40.10*	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*	40.74*	Started with 5 mg/d; increased to 10 mg/d in 1 week	
Liang et al[60]	Paliperidone ER	97.08	67.97*	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*	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[61]	Paliperidone ER	82		55.8+	Started with 6 mg/d; increased to 9 or 12 mg/d in 4–7 days. Final dose ranged from 3 to 12 mg/d according to clinical judgment	
	Olanzapine	76.6		63.8	Started with 10 or 20 mg/d; adjusted to 5–20 mg/d according to clinical judgment	

Notes: Versus baseline: *$P<0.05$; **$P<0.01$; ***$P<0.0001$. 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 al[17]	RCT	Paliperidone ER	46.8		47.9	54.6*			60.3*,+		
		Risperidone	47.2		48.1	52.7*			55.1*		
Su et al[46]	RCT	Paliperidone ER	45.57					64.46*	74.32*,+		
		Risperidone	44.12					63.32*	59.87*		
Ren et al[47]	RCT	Paliperidone ER	31.77			48.72*,+					
		Risperidone	32.54			37.67					
Zhou et al[48]	RCT	Paliperidone ER	27.98					52.34+			
		Risperidone	28.52					42.06			
Li et al[49]	RCT	Paliperidone ER	56.87			69.78*	78.59*,+				
		Risperidone	57.35			61.38	66.57*				
Yuan et al[51]	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 al[56]	RCT	Paliperidone ER	32.75					51.58**,+	68.85**,++		
		Olanzapine	31.47					45.03**	60.13**		
Liang et al[60]	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 al[62]	RCT	Paliperidone ER	32.75					52.68**,+	69.87**,++		
		Aripiprazole	32.47					46.05**	61.24**		
Zhou et al[63]	RCT	Paliperidone ER	45.2					78.0**,++			
		Aripiprazole	46.5					55.1			
Liu et al[10]	RCT	Paliperidone ER	50.72			66.91**			71.89**	78.87**	++ versus paliperidone ER $P<0.01$
		Typical antipsychotics	51.57			58.25++			52.68++	52.00++	
		Atypical antipsychotics	50.51			58.32++			68.30++	70.89++	
Huang et al[69]	Single arm	Paliperidone ER	47.07						56.61*		
Shi et al[14]	Single arm	Paliperidone ER	54.3							73.4**	
Si et al[70]	Single arm	Paliperidone ER	41.4			66.9		75.5**			
Yang et al[71]	Single arm	Paliperidone ER	47.0						56.6		
Wang et al[72]	Single arm	Paliperidone ER	52.28		64.44**	70.36**					
Zhou et al[73]	Single arm	Paliperidone ER	39.5	52.5**	62.6**	70.5**		72.6**			
Sun et al[74]	Single arm	Paliperidone ER	33.57						58.46**	71.32**	
Wang et al[23]	Single arm	Paliperidone ER	51.26	61.13**	61.17**	69.43**		73.52**			
Zhang et al[75]	Single arm	Paliperidone ER	58.6					72.4**	74.5**		

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 of PP for its introduction to the Chinese market.[29] It was a noninferiority-design, open-label, rater-blinded, parallel-group, 13-week study. The active comparator was risperidone long-acting injectable (RIS-LAI, 25–50 mg/2 weeks). A significant improvement with respect to baseline was observed at the end point for both groups; mean (standard deviation) change from baseline to end point in PANSS total scores was −23.6 (16.28) for the PP group and −26.9 (15.43) for the RIS-LAI group. The mean change in PSP was 16.8 (PP group) and 18.6 (RIS-LAI group), and the overall incidence of TEAEs was not different between the groups.

Three subsequent small sample size, open-label, randomized, comparative studies of PP and oral risperidone were conducted with the recommended initiation dosing regimen for PP over durations of 6, 8, and 12 weeks.[30–32] The mean change from baseline to end point in PANSS total score and the tolerability were comparable between both groups. A total of three single-arm studies of PP was conducted 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

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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
Paliperidone ER										
Paliperidone ER compared with risperidone										
Liu et al[11]	CC	RCT	OL	Observer expectation	First-episode	31.24, 32.04	54.0	Efficacy, effectiveness	PANSS	PANSS, WCST, CPT, CT, WMS-R
Li et al[17]	CC	RCT	NR	Blinding, noncompleters excluded		20–59		Efficacy, effectiveness, safety	PANSS	PANSS, ESRS, SF36, PSP, metabolic measures, prolactin, adverse events
Su et al[46]	CC	RCT	OL	Observer expectation		34.7, 35.4	48.9	Efficacy, effectiveness, safety	PANSS, PSP	PANSS, PSP, MSQ, adverse events
Ren et al[47]	CC	RCT	NR	Blinding		30.4, 31.2	63.2	Efficacy, effectiveness, safety	PANSS	PANSS, PSP, adverse events
Zhou et al[48]	CC	RCT	NR	Blinding, noncompleters excluded	First-episode	27.6, 26.9	47.2	Efficacy, effectiveness, safety	PANSS	PANSS, PSP, adverse events
Na et al[20]	CC	RCT	OL	Observer expectation		33.7, 34.5	48.8	Efficacy, safety	PANSS	PANSS, prolactin, metabolic measures, TESS
Li et al[49]	CC	RCT	NR	Blinding	Adolescent	16.61	41.2	Efficacy, effectiveness, safety	PANSS	PANSS, TESS, laboratory examination, PSP
Zhang et al[50]	CC	RCT	NR	Blinding, noncompleters excluded		32, 33	46.2	Efficacy, safety	PANSS	PANSS, TESS
Yuan et al[51]	CC	RCT	NR	Blinding, noncompleters excluded		33.1, 34.5	56.5	Efficacy, effectiveness	PANSS	PANSS, CGI, PSP
Li et al[52]	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[53]	CC	RCT	OL	Observer expectation	First-episode, female	27.08, 26.00	0.0	Efficacy, safety	BPRS	BPRS, TESS
Liu et al[54]	CC	RCT	DB		First-episode	29, 30	53.3	Efficacy, safety	PANSS	PANSS, TESS, metabolic measures, prolactin
Wang et al[18]	CC	RCT	OL	Observer expectation		35, 37	45.7	Efficacy, effectiveness, safety	PANSS	PANSS, SDSS, TESS
Paliperidone ER compared with olanzapine										
Hu et al[21]	Int	RCT	OL	Observer expectation, noncompleters excluded		25.24, 28.65	69.1	Efficacy, safety	PANSS, metabolic measures	PANSS, metabolic measures, adverse events, prolactin
Zhu et al[24]	CC	RCT	NR	Blinding	Refractory	42.7, 43.5		Efficacy, safety	PANSS	PANSS, TESS, metabolic measures
Xie et al[56]	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[57]	CC	RCT	NR	Blinding		38.6, 39.4	53.2	Efficacy, safety	BPRS	BPRS, TESS

Cao et al[58]	CC	RCT	NR	Blinding		26.00, 27.12	53.2	Efficacy, safety	PANSS	PANSS, TESS
Su et al[59]	CC	RCT	NR	Blinding		31.0, 32.0	51.5	Efficacy, safety	BPRS	BPRS, SAPS, TESS
Liang[60]	CC	RCT	OL	Observer expectation, noncompleters excluded		30.42, 29.47	53.9	Efficacy, effectiveness, safety	PANSS	PANSS, PSP, TESS
Guo et al[61]	CC	RCT	NR	Blinding		35.8, 33.6	68.3	Efficacy, safety	Liver function	Liver function, PANSS, TESS
Zhang et al[22]	CC	RCT	DB			33, 34	54.2	Efficacy, safety	PANSS	PANSS, CGI-S, adverse events, metabolic measures, VAS, AIMS, BARS, SAS, prolactin
Paliperidone ER compared with aripiprazole										
Zhang et al[9]	Int	RCT	OL	Observer expectation, noncompleters excluded	First-episode	27.1, 25.7, 26.3	38.9	Efficacy, safety	PANSS, metabolic measures	PANSS, CGI-S, metabolic measures
Xie et al[62]	CC	RCT	NR	Blinding, noncompleters excluded	First-episode, adolescent	14, 15	52.4	Efficacy, effectiveness, safety	PANSS	PANSS, PSP, TESS
Zhou et al[63]	CC	RCT	NR	Blinding	Male	35.8, 35.5	100.0	Efficacy, effectiveness, safety	PANSS, sexual function	PANSS, PSP, sexual function, prolactin
Paliperidone ER compared with clozapine										
Luo et al[12]	CC	RCT	NR	Blinding		33.4, 32.9	51.7	Efficacy, effectiveness, safety	PANSS	PANSS, TESS, WHOQOL·100, SDSS, WMS-R
Liu et al[64]	CC	RCT	OL	Observer expectation	Refractory	41.46, 39.84	58.0	Efficacy, safety	PANSS	PANSS, TESS
Paliperidone ER compared with ziprasidone										
Zhang et al[9]	Int	RCT	OL	Observer expectation, noncompleters excluded	First-episode	27.1, 25.7, 26.3	38.9	Efficacy, safety	PANSS, metabolic measures	PANSS, CGI-S, metabolic measures
He et al[19]	CC	RCT	DB	Noncompleters excluded		33.4, 32.8	52.9	Efficacy, effectiveness, safety	GQOLI-74	GQOLI-74, PANSS, TESS
Paliperidone ER compared with placebo										
Rui et al[8]	Int	RCT	DB			31.1, 32.3	40.7	Effectiveness, efficacy, safety	Relapse	Relapse, PANSS, CGI-S, TEAEs
Paliperidone ER compared with others										
Paliperidone ER compared with paliperidone ER + magnesium valproate										
Liu et al[65]	CC	RCT	NR	Blinding		36.0	76.1	Efficacy, safety	PANSS	PANSS, TESS
Paliperidone ER compared with typical antipsychotics and atypical antipsychotics										
Liu et al[10]	CC	RCT	NR	Blinding, noncompleters excluded, concomitant antipsychotics		33.91, 33.77, 34.04	52.0	Efficacy, effectiveness, safety	PANSS	PANSS, PSP, TESS
Paliperidone ER compared with paliperidone ER + aripiprazole										
Liang et al[66]	CC	RCT	DB	Noncompleters excluded		30.8, 30.3	37.5	Efficacy, safety	PANSS	PANSS, AIMS, BARNES, UKU, prolactin

(*Continued*)

Table S1 (*Continued*)

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
Paliperidone ER compared with paliperidone ER + escitalopram										
Yan et al[13]	CC	RCT	NR	Blinding		39.6, 38.4	51.2	Efficacy, effectiveness, safety	WAIS, WCST	PANSS, WAIS, WCST, TESS
Different dose groups of paliperidone ER										
Luo et al[67]	CC	RCT	NR	Blinding		18–62	52.5	Efficacy, safety	PANSS	PANSS, TESS, metabolic measures
Huang et al[69]	Int	Single-arm study	OL	Observer expectation		40.3	54.6	Efficacy, effectiveness, safety	PANSS	PANSS, PSP, social function score, adverse events
Tsai et al[76]	Int	Single-arm study	NR	Blinding		NR	NR	Effectiveness	DAI-10	DAI-10, CGI-S, PSP
Shi et al[14]	Int	Single-arm study	OL	Observer expectation		27.6	48.9	Efficacy, effectiveness, safety	PSP, MATRICS	PSP, MATRICS, PANSS, CGI-S, SAS, BARS, adverse events
Si et al[70]	Int	Single-arm study	OL	Observer expectation, noncompleters excluded	First-episode	30.0	50.0	Efficacy, effectiveness, safety	PSP	PSP, CGI-S, PANSS
Tang[77]	Int	Single-arm study	OL	Observer expectation		40.1	46.1	Efficacy	PANSS	PANSS
Yang et al[71]	Int	Single-arm study	OL	Observer expectation				Efficacy, effectiveness	PANSS, PSP	PANSS, PSP
Wang et al[72]	CC	Single-arm study	NR	Blinding, noncompleters excluded		18–40	69.2	Efficacy, effectiveness, safety	PANSS	PANSS, PSP, MSQ, adverse events
Li et al[78]	CC	Single-arm study	NR	Blinding, concomitant antipsychotic	Adolescent	14.4	43.6	Efficacy, safety	PANSS	PANSS, TESS, laboratory examination, prolactin
Wu et al[79]	CC	Single-arm study	OL	Observer expectation, noncompleters excluded		36.65	35.4	Efficacy, safety	PANSS, metabolic measures	PANSS, tolerability, metabolic measures
Zhou et al[73]	CC	Single-arm study	NR	Blinding		28.7	47.2	Efficacy, effectiveness, safety	PANSS	PANSS, PSP, metabolic measures, UKU, prolactin
Chen et al[15]	CC	Single-arm study	OL	Observer expectation		29.9	49.0	Effectiveness	HVLT	HVLT, BVMT-R, WAIS-III, WMS-III, Stroop, Digit Symbol-Coding, PASAT
Sun et al[74]	CC	Single-arm study	NR	Blinding, noncompleters excluded	First-episode, adolescent	13.5	54.1	Efficacy, effectiveness, safety	PANSS	PANSS, PSP, MSQ, TESS, metabolic measures
Zhang et al[16]	CC	Single-arm study	NR	Blinding, noncompleters excluded		35.89	45.2	Effectiveness	WCST	WCST, Stroop, TOH
Lv et al[80]	CC	Single-arm study	OL	Observer expectation, noncompleters excluded		39.03	46.7	Efficacy, safety	Metabolic measures	Metabolic measures, PANSS, CGI-S, adverse events
Wang et al[23]	CC	Single-arm study	NR	Blinding		22.87	43.5	Efficacy, effectiveness, safety	PANSS, prolactin	PANSS, PSP, adverse events, prolactin

Zhang et al[75]	CC	Single-arm study	OL	Observer expectation, noncompleters excluded		31	49.5	Efficacy, effectiveness, safety	PANSS	PANSS, CGI-S, PSP, ESRS, metabolic measures, prolactin
Liu et al[81]	CC	Single-arm study	NR	Blinding		40	53.8	Efficacy	PANSS	PANSS
Xiong et al[55]	CC	Observational study		Noncompleters excluded		28.6, 29.2	58.7	Efficacy, safety	PANSS	PANSS, TESS
Si et al[82]	Int	Pharmacokinetic study	NR	Blinding	Healthy	19–35	54.2	Pharmacokinetics, safety, tolerability	Pharmacokinetics	Pharmacokinetics
Paliperidone ER compared with paliperidone palmitate										
Jiang et al[68]	CC	RCT	NR	Blinding		32.7, 34.1	53.6	Efficacy, effectiveness, safety	PANSS	PANSS, TESS, PSP, MSQ
Paliperidone palmitate										
Paliperidone palmitate compared with risperidone										
Li et al[29]	Int	RCT	OL	Observer expectation		31.5, 32.0	32.8	Efficacy, effectiveness, safety	PANSS, PSP, CGI-S	PANSS, PSP, CGI-S, TEAEs
Ma et al[31]	CC	RCT	OL	Observer expectation, noncompleters excluded	Adolescent	16.05, 15.57	51.0	Efficacy, effectiveness, safety	PANSS	PANSS, PSP, CGI-S, adverse events
Yi et al[32]	CC	RCT	OL	Observer expectation, noncompleters excluded		31.5, 35.5	42.6	Efficacy, safety	PANSS	PANSS, TESS
Paliperidone palmitate compared with placebo										
Wakamatsu et al[30]	Int	RCT	DB			45		Efficacy, safety	PANSS	PANSS, CGI-S, TEAEs
Zhang et al[34]	Int	Single-arm study	OL	Observer expectation	Recent-onset	28.7	65.5	Efficacy, effectiveness, safety	PANSS	PANSS, CGI-SCH, MSQ, hospitalization
Miao et al[35]	CC	Single-arm study	OL	Observer expectation, noncompleters excluded, concomitant antipsychotics		33.2	39.7	Efficacy, safety	PANSS	PANSS, CGI-S, TESS
Bressington et al[33]	Int	Retrospective observational study		Retrospective		40.86	71.2	Effectiveness	Hospitalization rate	Hospitalization rate
Si et al[25]	Int	Pharmacokinetic study	OL	Observer expectation		53	76.6	Pharmacokinetics, efficacy	Pharmacokinetics	Pharmacokinetics, PANSS, CGI-S
Li et al[26]	CC	Pharmacokinetic study	NR	Blinding, noncompleters excluded		25.44	44.4	Pharmacokinetics, efficacy, safety	Pharmacokinetics, PANSS	Pharmacokinetics, PANSS, adverse events, laboratory examination

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-Severity; CGI-SCH, Clinical Global Impression of Schizophrenia; CPT, Continuous Performance Task; CT, Number Cancellation Test; DAI-10, The Drug Attitude Inventory; DB, double-blind; ER, extended-release; ESRS, 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; SAPS, scale for assessment of positive symptoms; SAS, 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 Undersogelser 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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