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Meta-Analysis of the Effect of Blonanserin in Treating Patients with Schizophrenia

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ABSTRACT

Introduction: This study aimed to investigate the efficacy and safety of blonanserin in patients with schizophrenia.

Methods: Electronic databases (PubMed, Web of Science, Cochrane Library, Embase) were searched. Studies evaluating the efficacy and safety of blonanserin in treating schizophrenia were inclued. The combined effect sizes were calculated using relative risk (RR), risk difference (RD) or mean difference (MD).

Results: Overall, 13 prospective studies involving 2,479 patients with schizophrenia were summarised and analysed. We selected five commonly used antipsychotic drugs, namely haloperidol, risperidone, olanzapine, paliperidone and aripiprazole. The meta-analysis showed that compared with a placebo, blonanserin significantly improved the Positive and Negative Syndrome Scale (PANSS) total scores (MD: -7.91; 95% confidence interval [CI]: -15.56, -0.26) and positive scores (MD: -2.48; 95% CI: -4.79, -0.18), and it was comparable with other Antipsychotic drugs regarding PANSS total scores, positive scores and general psychopathology scores. Additionally, the difference between blonanserin and haloperidol (MD: -0.75; 95% CI: -1.00, -0.50) on PANSS negative score changes was statistically significant. At the same time, the safety analysis revealed that compared with risperidone, blonanserin was associated with a lower risk of increased blood prolactin (RR: 0.66; 95% CI: 0.51, 0.86), hyperprolactinemia (RR: 0.30; 95% CI: 0.11, 0.78) and weight gain (RD: -0.04; 95% CI: -0.07, -0.01) as well as a higher risk of akathisia (RD: 0.10; 95% CI: 0.04, 0.17). Moreover, it exhibited side-effects similar to those of other antipsychotic drugs regarding constipation, dizziness, headache, insomnia, muscle rigidity and hypersalivation.

Conclusion: Blonanserin is effective and safe in the treatment of schizophrenia, which is beneficial for guiding the clinical practice of schizophrenia treatment. However, more high-quality studies are needed in the future to validate its effect.

Keywords: Blonanserin, meta-analysis, schizophrenia

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INTRODUCTION

Schizophrenia is a common mental disorder characterised by chronic or recurrent disorders of thinking, affect, behaviour and cognition and is a major contributor to the global burden of disease, with a global prevalence of approximately 1% (1,2). Patients with schizophrenia usually require lifelong therapeutic interventions, and medication has been identified as the primary treatment, with antipsychotics being the main first-line medication (3,4).

Blonanserin is a novel atypical antipsychotic drug approved in countries including Japan, Korea and China, with a high affinity for dopamine D2, D3 and 5-HT2A receptors (5,6). Some studies suggest that D3 receptors may be a prospective therapeutic target for the treatment of cognitive impairment associated with schizophrenia (7,8). Meanwhile, in another study, the brain/plasma concentration ratio of blonanserin in patients with schizophrenia was 3.38, indicating a satisfactory blood–brain barrier permeability (9). Therefore, blonanserin theoretically boasts the advantage of improving cognitive function in the clinical treatment of schizophrenia. Additionally, data from clinical trials have revealed that blonanserin exhibits higher safety and efficacy (10). However, only four studies were included in the previous meta-analysis (11), which excluded the most recent randomised controlled studies comparing the effects of blonanserin.

Highlights

- **Compared with a placebo, blonanserin significantly improved the PANSS total scores.**
- **The PANSS negative score changes between blonanserin and haloperidol were significant.**
- **Blonanserin was associated with a lower risk of increased blood prolactin.**
- **Blonanserin had side-effects similar to other antipsychotics.**
- **Blonanserin is effective and safe in the treatment of schizophrenia.**

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The meta-analysis in the current study involves a systematic review of two interventions based on direct comparisons of randomized controlled trials. We select five commonly used antipsychotic drugs (haloperidol, risperidone, olanzapine, paliperidone, aripiprazole) and blonanserin in randomised controlled trials to explore the differences between the efficacy and safety of these drugs and provide strong evidence for clinical decision-making. Given this, the study is designed to investigate the efficacy and safety of blonanserin in patients with schizophrenia through a systematic review.

METHODS

Search Strategy

Following the PRISMA 2020 statement (12), a total of four electronic databases (PubMed, Web of Science, Cochrane Library and Embase) were systematically searched from inception to 1 March 2024. The retrieval strategy for the English databases was as follows: ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia s"[All Fields]) AND ("blonanserin"[Supplementary Concept] OR "blonanserin"[All Fields]). Additionally, the target articles were obtained by reviewing the references of the included articles and relevant reviews.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1) The studies published in peer-reviewed journals in English; 2) study participants with no age, race or gender restrictions and patients with an identified diagnosis of schizophrenia; 3) the intervention group was treated with blonanserin monotherapy, with no dosage or dose restrictions; 4) the control group was a blank control, placebo control, before-and-after self-control or the use of other types of antipsychotics; 5) prospective studies, including randomised controlled trials and cohort studies.

The exclusion criteria were as follows: 1) study participants with severe hepatic or renal dysfunction; 2) study participants who concomitantly took other antipsychotics, except lorazepam for the treatment of clinically significant symptoms of agitation.

Literature Screening and Data Extraction

Literature screening was performed independently by two researchers, with a third researcher intervening to resolve any disagreements in the screening results. The data were extracted using the standard data extraction form developed by the research team, including the following data: 1) basic data about the article: first author, time of publication and region; 2) study design: type of study, sample size and duration of follow-up; 3) study population: mean age, % male and diagnosis of the disease; 4) interventions: name of the medication, formulations and dosage; and 5) outcomes: the effectiveness of the intervention was evaluated using the Positive and Negative Syndrome Scale (PANSS), which included the total scores, positive scores, negative scores and general psychopathology scores; the safety of the intervention was evaluated using the incidence of adverse events.

Evaluation of Literature Quality

The quality of literature containing randomised controlled trials was evaluated using the Cochrane risk of bias tool (13). Evaluation with this method mainly involved the method of randomisation, allocation scheme concealment, blinding, completeness of outcome data, selective reporting of study results and other risks of bias.

Statistical analysis methods

RevMan 5.3 (The Cochrane Collaboration, Washington, US) was used for the data analysis. Measurement data were expressed as mean difference (MD), and effect sizes for count data were expressed as relative risk (RR). For any zero-events in the included studies (14), a meta-analysis was performed using risk difference (RD), and 95% confidence intervals (CIs) were adopted to estimate the interval ranges for effect sizes. Since random-effects models are more conservative than fixed-effects models, conservative models were utilized to address the possibility of potential effect differences across studies and populations (13,15). Subgroup analyses were performed according to the different antipsychotic drugs used in the control group; previous studies suggested the risk of sedative effects as the only difference among these drugs (16). Therefore, a meta-analysis was performed on comparable medications with the same effects as paliperidone and risperidone. Meanwhile, the presence and magnitude of heterogeneity were identified through the heterogeneity test using the Q-test and I^2 statistics, with I^2 <50% or p >0.05 suggesting satisfactory homogeneity between the included studies. The Egger and Begg tests were utilized for the publication bias test. The significance level was set at 0.05 unless otherwise specified.

RESULTS

Literature Screening and Basic Characteristics of Included Studies

After searching publicly available electronic databases, a total of 435 studies were included in the literature review process, as shown in Fig. 1. A total of 201 duplicate studies and 156 irrelevant studies were excluded, and a total of 234 articles were included in the full-text review process. Finally, 13 eligible studies were included following the inclusion and exclusion criteria of this study (10,17–28). Basic information about the included studies is shown in Table 1. The 13 studies were published between 2009 and 2022, with 8 conducted on the Japanese population, 2 on the Korean population and 1 on the Chinese population, while the other 2 studies involved multinational populations with 2.479 patients with schizophrenia. Two studies were conducted on non-adults, with a duration of 6–52 weeks. Five commonly used antipsychotic drugs (haloperidol, risperidone, olanzapine, paliperidone, aripiprazole) were selected and compared with blonanserin in randomised controlled trials to explore the differences between the efficacy and safety of these drugs and provide strong evidence for clinical decision-making. In terms of interventions used in the control group, two studies were three-arm studies, four studies used a placebo control, four studies used risperidone, two studies used aripiprazole, or haloperidol, respectively. Additionally, one study used olanzapine or paliperidone, respectively.

Quality of Included Studies

Literature quality was evaluated for the included studies using the Cochrane risk of bias tool. Among them, one was an experimental study with a high risk of bias in terms of randomisation, allocation concealment and blinding and two were randomised control trials (RCTs) with a high risk of bias due to no blinding performed. Meanwhile, other RCTs were of high quality, as shown in Fig. 2 and Fig. 3.

PANSS Total Scores

Eleven articles provided 13 data on the effect of blonanserin on the PANSS total score, involving 1.954 patients with schizophrenia. The subgroup analysis by different antipsychotic drugs used in the control group revealed a similar effect of blonanserin on the PANSS total score changes compared with risperidone/paliperidone (MD: -0.27; 95% CI: -3.98, 3.44), haloperidol (MD: -0.07; 95% CI: -5.22, 5.09) and aripiprazole (MD: 0.84; 95% CI: -3.52, 5.19). Blonanserin also significantly improved the PANSS total score changes (MD: -7.91; 95% CI: -15.56, -0.26) compared with the placebo. Additionally, Niitsu et al. (25) found that

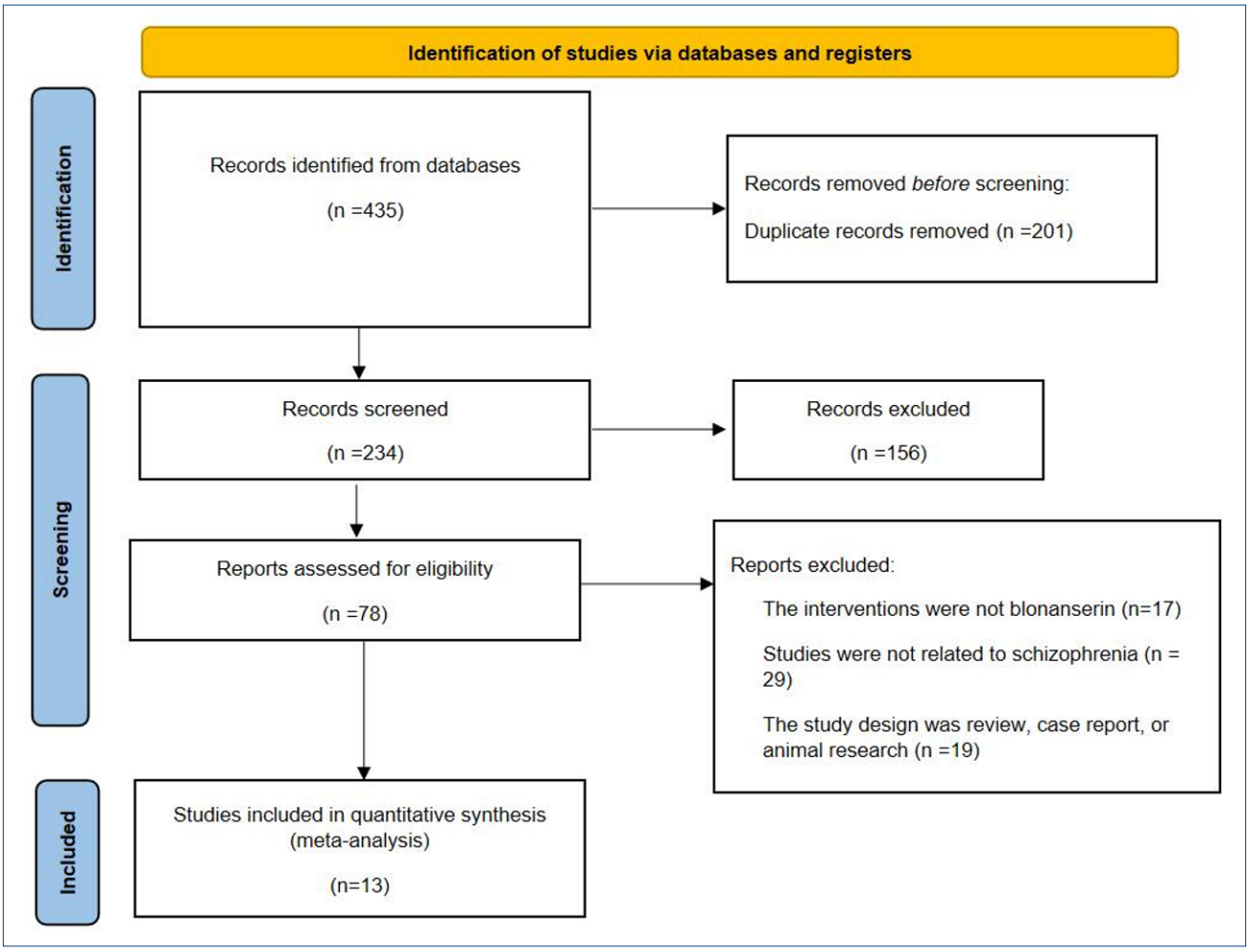

Figure 1. Flow chart of research screening

the difference in PANSS total score change of blonanserin was similar to olanzapine (p=0.42) (Fig. 4).

Positive and Negative Syndrome Scale Subscales

Subgroup analyses for the effect of blonanserin on changes in the total scores of the PANSS positive scale, negative scale and general psychopathology scale suggested a similar effect of blonanserin on the changes in the total PANSS positive scores compared with risperidone/paliperidone (MD: -0.02; 95% CI: -0.66, 0.62), haloperidol (MD: 0.84; 95% CI: -1.36, 3.03) and aripiprazole (MD: 0.01; 95% CI: -1.07, 1.09), along with a more significant effect than the placebo (MD: -2.48; 95% CI: -4.79, -0.18), as shown in Fig. 5. Additionally, the difference in the PANSS positive scores between blonanserin and olanzapine was not statistically significant (25).

For the effect on changes in the total PANSS negative scores, the difference between blonanserin and haloperidol (MD: -0.75; 95% CI: -1.00, -0.50) was statistically significant, as shown in Fig. 6. Analysis of changes in the PANSS general psychopathology scores showed that blonanserin exhibited similar effects to risperidone/paliperidone (MD: -0.21; 95CI: -2.20, 1.79) and aripiprazole (MD: -0.61; 95% CI: -3.10, 1.87), as shown in Fig. 7. Niitsu et al. (25) found that the difference in the PANSS negative scores between blonanserin and olanzapine was not statistically significant.

Adverse Events

A meta-analysis of the effect of blonanserin on total adverse events showed a similar effect of blonanserin to risperidone (RR: 0.99; 95% CI: 0.97, 1.01), haloperidol (RR: 0.81; 95% CI: 0.51, 1.29) and aripiprazole (RR: 0.89; 95% CI: 0.56, 1.43). Results from Niitsu et al. (25) indicated that the incidence of treatment-emergent adverse events was the same (34.6% vs 34.6%) between blonanserin and olanzapine (Fig. 8).

The effect of blonanserin on different adverse events is shown in Table 2. Compared with risperidone (RD: 0.10; 95% CI: 0.04, 0.17), blonanserin was associated with a higher risk of akathisia but exhibited a lower risk than that of haloperidol (RD: -0.14; 95% CI: -0.22, -0.06). Compared with risperidone, blonanserin was associated with a lower risk of increased blood prolactin (RR: 0.66; 95% CI: 0.51, 0.86), hyperprolactinemia (RR: 0.30; 95% CI: 0.11, 0.78) and weight gain (RD: -0.04; 95% CI: -0.07, -0.01). Moreover, there was also a lower risk of tremor with blonanserin than with haloperidol (RD: -0.16; 95% CI: -0.24, -0.08). Furthermore, blonanserin has effects similar to those of other antipsychotic drugs regarding constipation, dizziness, headache, insomnia, muscle rigidity and hypersalivation.

Publication Bias

The publication bias was tested using Egger and Begg tests. The results indicated that there were no significant publication bias exited in included studies, with all p values greater than 0.05.

Table 1. Basic characteristics of eligible studies

Study	Location	Study design	Diagnostic criteria	Mean age (experimental/control)	Male % (experimental/control)	Intervention	Comparison	Treatment course	Sample size
Garcia, 2009	USA, Bulgaria, Czech Republic, Russia	RCT	DSM-IV-TR	37.91±10.89/38.1±11.4/38.6±11.5	59.02/58.3/62.5	formulation: tablet dosage: 2.5 mg, 5 mg, 10 mg	(1) placebo, (2) haloperidol, 10 mg	6 weeks	183/60/64
Yang, 2010	Koera	RCT	ICD-10	34.46±10.35/35.97±10.15	51.09/47.25	formulation: tablets dosage: 8 mg/d	risperidone, 2 mg/d	8 weeks	92/91
Hori, 2014	Japan	RCT	DSM-IV-TR	29.6±8.3/31.1±8.8	45/47.4	formulation: tablet dosage: 14.6±4.0 mg/d	risperidone, 3.1±1.3 mg/d	8 weeks	20/19
Li, 2015	China	RCT	DSM-IV-TR	33.62±11.02/35.02±10.80	45.31/56.39	formulation: tablets dosage: 8–24 mg/d	risperidone tablets, 2–6 mg/day	8 weeks	128/133
Kishi, 2016	Japan	RCT	DSM-IV-TR	36.5±9.72/42.4±12.6	50.0/31.8	formulation: tablets dosage: 4–24 mg/d	aripiprazole, 6–30 mg/d	24 weeks	22/22
Harvey, 2019	Japan	RCT	ICD-10	41.9±12.7/42.9±13.2	58.1/59.1	formulation: tablets dosage: 8–24 mg/d	haloperidol, 4–12 mg/d	8 weeks	129/132
Woo, 2019	Koera	quasi experiment	DSM-IV-TR	46.4±9.9	61.5	formulation: tablets dosage: 4–24 mg/d	before and after control	12 weeks	52/52
Iwata, 2020	Japan, China, Korea, Malaysia, Philippines, Russia, Ukraine	RCT	DSM-5	40.65±13.79/41.5±13.7	59.23/59.5	formulation: patch dosage: 40 mg/d, 80 mg/d	placebo	6 weeks	231/190
Harvey, 2020	Japan	RCT	ICD-10	45.0±14.8/46.0±14.5	56.4/52.1	formulation: tablets dosage: 8–24 mg/d	risperidone, 2–6 mg/d	8 weeks	156/144
Niitsu, 2020	Japan	RCT	DSM-IV-TR, DSM-5	49.5±8.2/47.0±6.4	53.85/61.54	formulation: tablet dosage: 8–24 mg/d	olanzapine, 5–20 mg/d	24 weeks	26/26
Ishigooka, 2022	Japan	RCT	DSM-IV-TR	46.7±12.6/48.0±14.1/45.0±13.2	56.5/51.2/51.2	formulation: tablet dosage: 8–24 mg/d	(1) aripiprazole, 12–30 mg/d (2) paliperidone, 6–12 mg/d	52 weeks	85/82/84
Saito, 2022(a)	Japan	RCT	DSM-IV-TR	15.5±1.58/15.7±1.75	44.3/38.9	formulation: tablet dosage: 4–24 mg/d	placebo	52 weeks	70/36
Saito, 2022(b)	Japan	RCT	DSM-IV-TR	15.45±1.59/15.6±1.69	42.72/42.6	formulation: tablet dosage: 8–16 mg/d	placebo	6 weeks	103/47

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

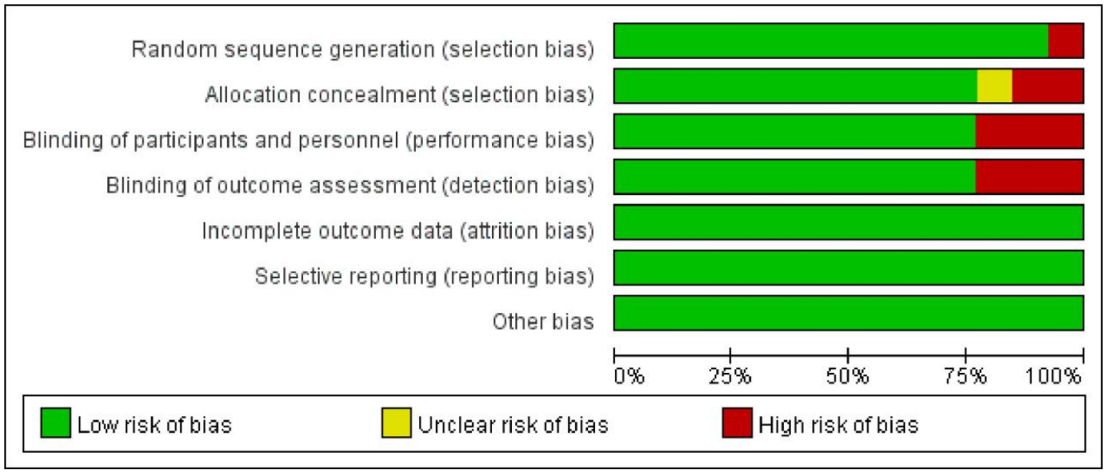

Figure 2. Risk of bias graph.

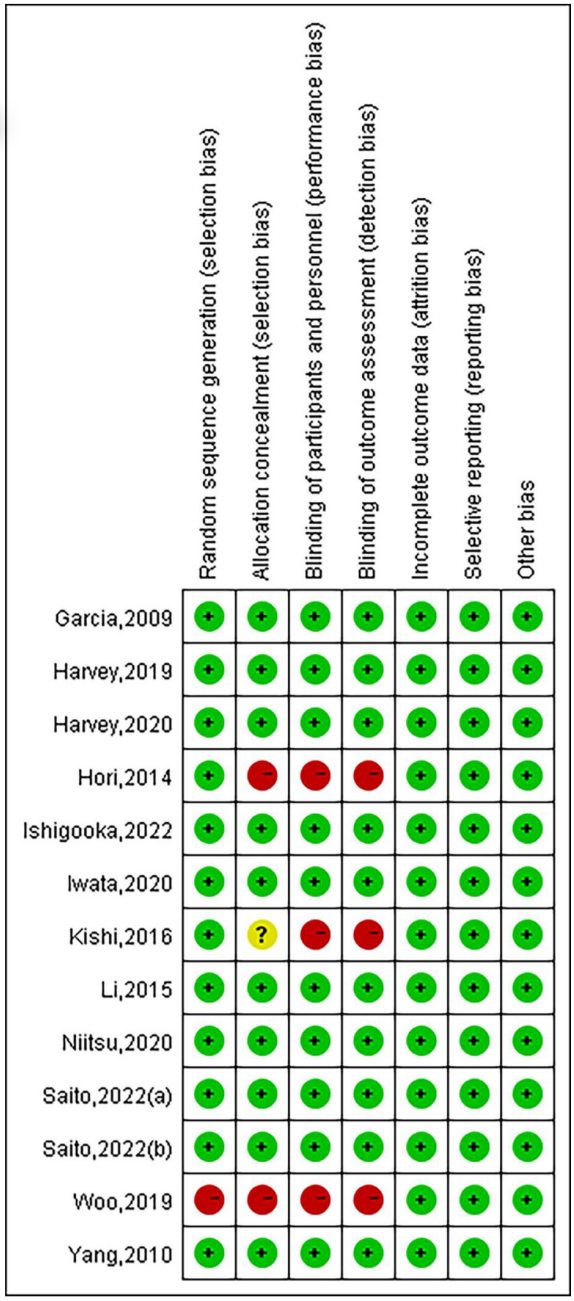

Figure 3. Risk of bias summary.

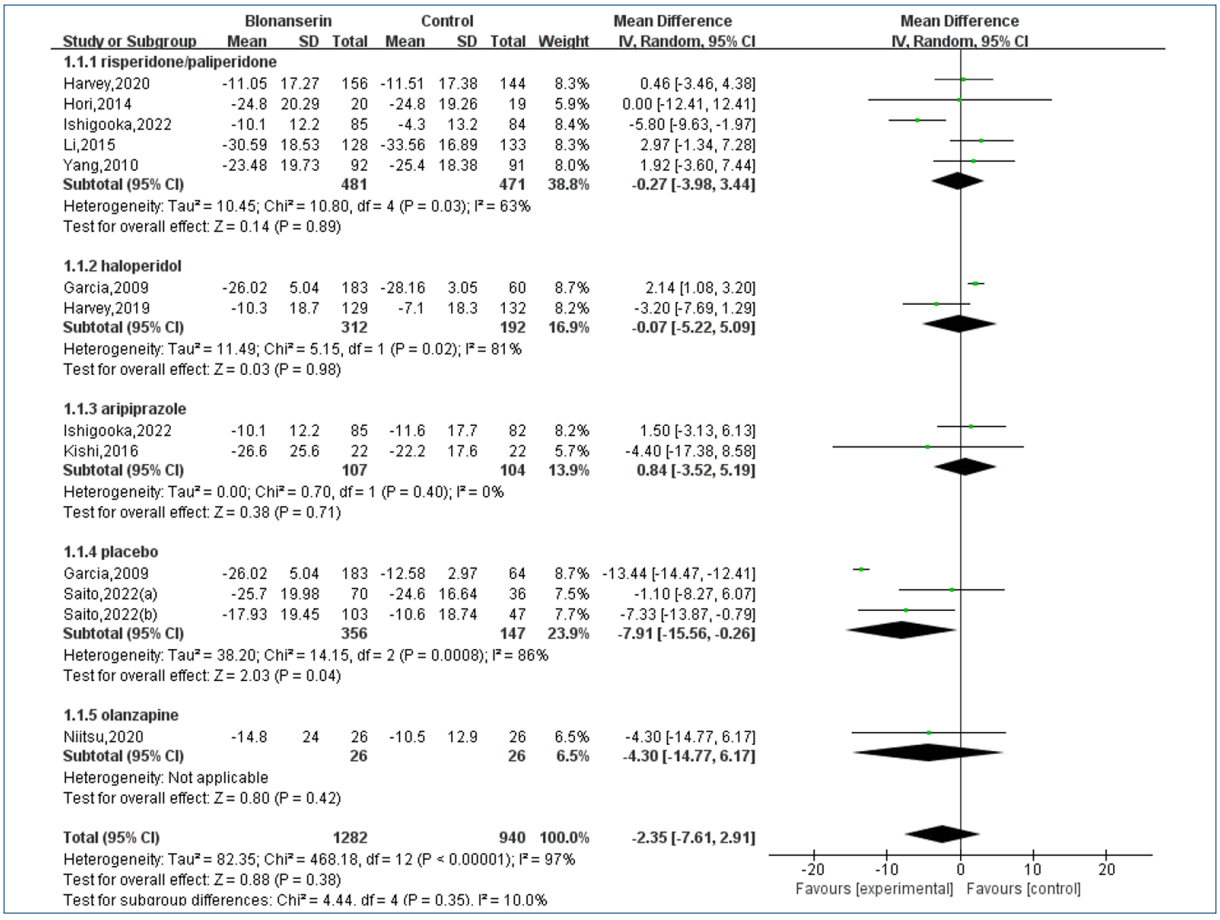

Figure 4. Efficiency of blonanserin on PANSS total scores compared with placebo or other anti-schizophrenic drugs.
SD: Standard Deviation, CI: Confidence Interval, IV: Inverse Variance.

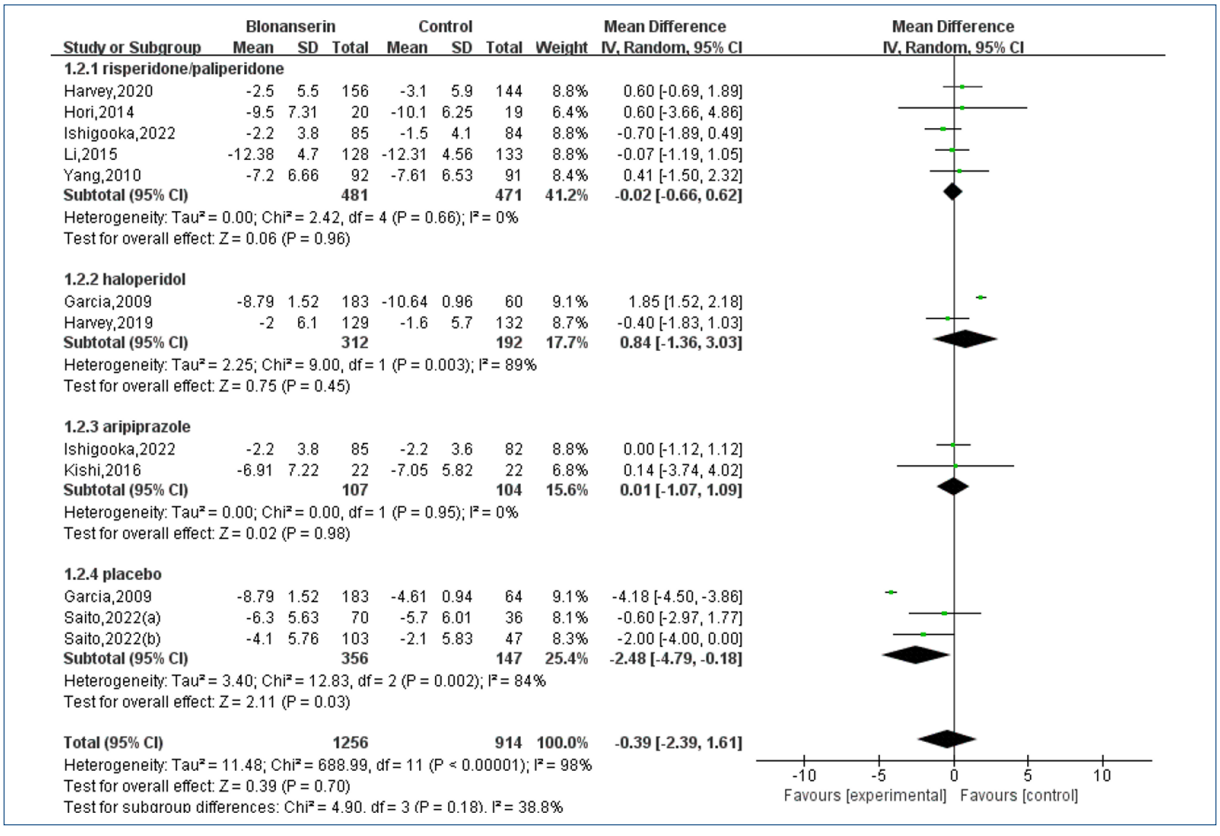

Figure 5. Efficiency of blonanserin on PANSS positive scores compared with placebo or other anti-schizophrenic drugs.
SD: Standard Deviation, CI: Confidence Interval, IV: Inverse Variance.

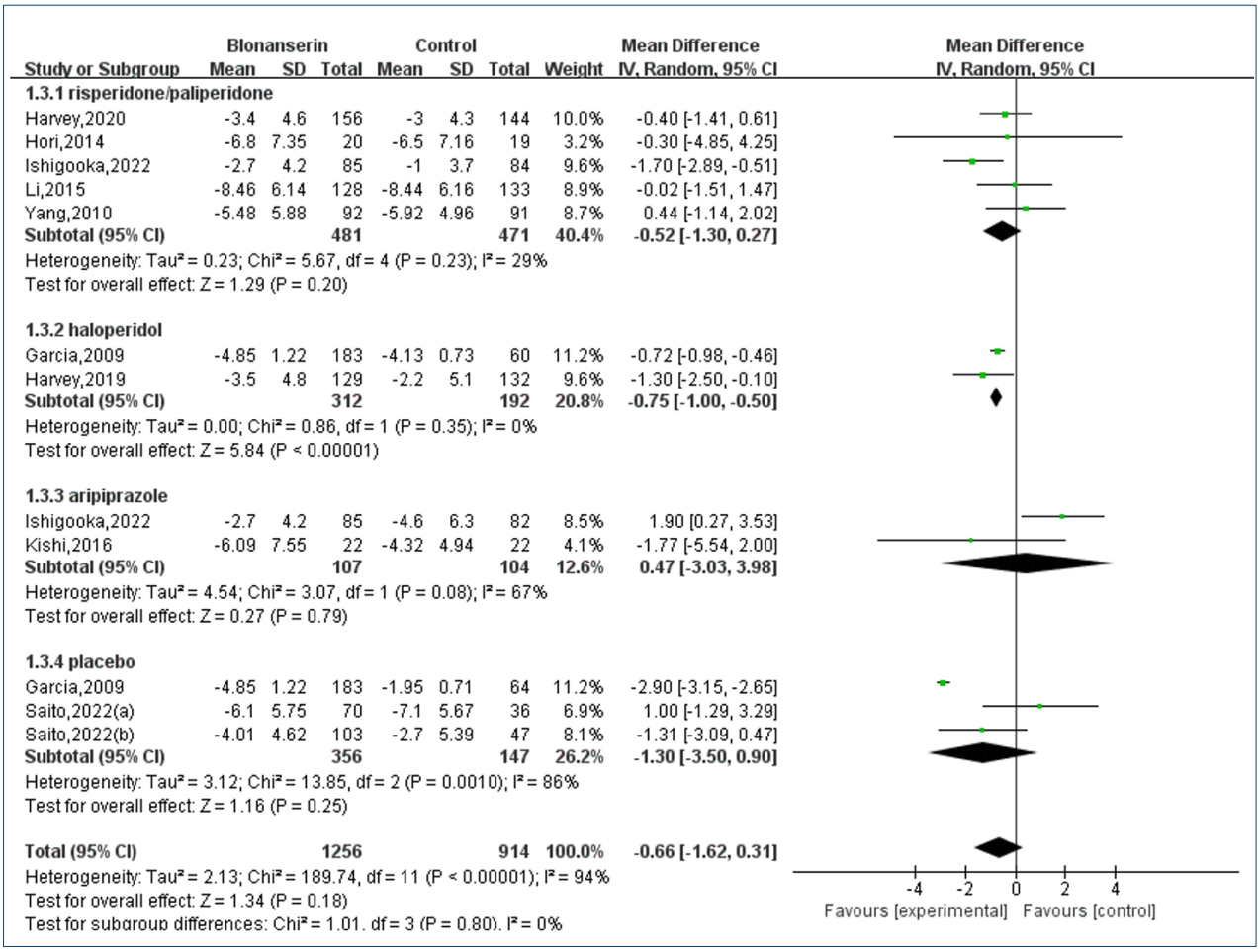

Figure 6. Efficiency of blonanserin on PANSS negtive scores compared with placebo or other anti-schizophrenic drugs.
SD: Standard Deviation, CI: Confidence Interval, IV: Inverse Variance.

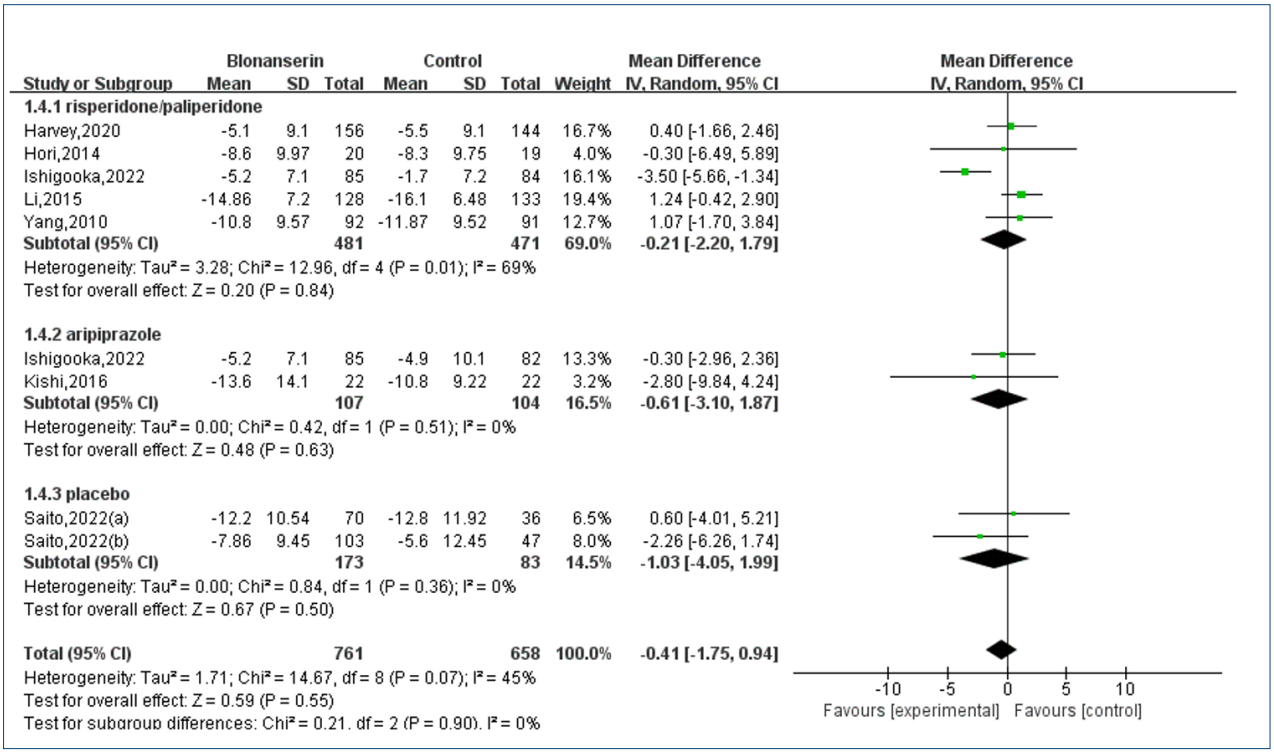

Figure 7. Efficiency of blonanserin on PANSS general scores compared with placebo or other anti-schizophrenic drugs.
SD: Standard Deviation, CI: Confidence Interval, IV: Inverse Variance.

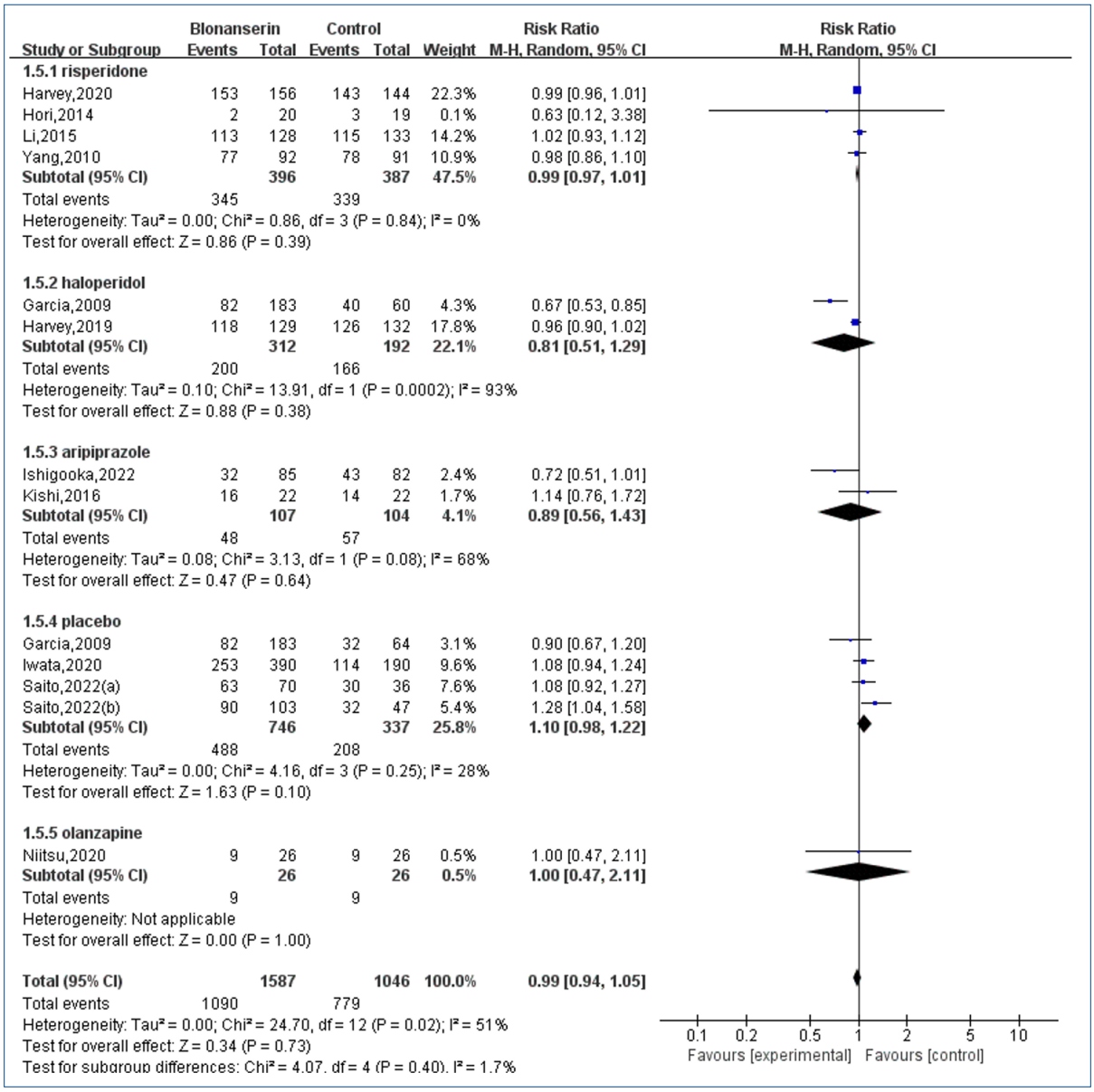

Figure 8. Efficiency of blonanserin on total adverse event compared with placebo or other anti-schizophrenic drugs.
SD: Standard Deviation, CI: Confidence Interval, IV: Inverse Variance.

DISCUSSION

An updated systematic review and meta-analysis of randomised controlled studies comparing blonanserin and other antipsychotic drugs were conducted in this study, thereby providing critical evidence for demonstrating the efficacy and safety of blonanserin in treating patients with schizophrenia. Specifically, the analysis of 13 prospective studies involving 2.479 patients with schizophrenia suggested that blonanserin significantly improves the PANSS total and positive scores compared with a placebo, and the difference between blonanserin and haloperidol on PANSS negative scores was significant. There was no difference in the efficacy of blonanserin compared with the placebo and it exhibited efficacy comparable with other antipsychotic drugs (risperidone/paliperidone, aripiprazole), along with satisfactory safety.

This study is consistent with previous findings. A reticular meta-analysis was conducted by Kishi et al. (29) on the efficacy and safety of antipsychotics in the treatment of schizophrenia, and the results after being adjusted for direct and indirect comparisons revealed an efficacy and safety of blonanserin similar to other antipsychotics (risperidone, aripiprazole, clozapine, clocapramine, mosapramine, paliperidone). The current meta-analysis indicated that blonanserin exhibited similar efficacy to other antipsychotics on the PANSS total and positive scores but was superior to haloperidol in improving the PANSS negative scores. There is no difference between a placebo and blonanserin regarding efficacy, which is consistent with the findings from another study by Kishi et al. (11). Previous studies demonstrated that blonanserin is associated with low risk of weight gain and hyperprolactinemia, which are associated with some second-generation antipsychotic drugs. Weight gain in patients with schizophrenia is mainly attributed to decreased activity due to the underlying illness, as well as the antagonistic actions of serotonin 5-HT2 c, histamine H1 and muscarinic M3 receptors of second-generation antipsychotics (30). Poor medication adherence is mainly associated with weight gain (31,32). Post-marketing surveillance in Japan indicated that the incidence of hyperprolactinemia was 4.6% for a long-term surveillance study (33) and 2.8% for a 12-week surveillance study (34).

Table 2. Effect of blonanserin on different adverse event compared with other antipsychotics

Adverse event	Comparison	Studies	N	RR/RD	95%CI	P	I2
Akathisia[a]	risperidone	3	522	0.10	0.04, 0.17	0.030	0%
	haloperidol	2	504	-0.14	-0.22, -0.06	<0.001	0%
	aripiprazole	2	211	-0.02	-0.09, 0.05	0.580	0%
	placebo	4	1083	0.08	0.03, 0.13	0.002	53%
Blood prolactin increased	risperidone	3	744	0.66	0.51, 0.86	0.020	61%
	placebo	2	256	1.57	0.26, 9.35	0.620	58%
Constipation	risperidone	3	744	0.90	0.63, 1.28	0.550	0%
	aripiprazole	2	211	1.63	0.41, 6.47	0.490	0%
	placebo	2	686	1.24	0.58, 2.63	0.580	0%
Dizziness[a]	risperidone	2	483	-0.03	-0.12, 0.07	0.560	76%
	aripiprazole	2	211	-0.01	-0.04, 0.02	0.560	0%
Headache	risperidone/paliperidone	3	652	1.03	0.64, 1.68	0.890	0%
	placebo	3	977	0.75	0.30, 1.85	0.530	54%
Hyperprolactinemia	risperidone	2	483	0.30	0.11, 0.78	0.010	8%
	placebo	2	256	1.94	0.21, 17.46	0.560	72%
Insomnia	risperidone	3	744	1.22	0.96, 1.56	0.110	0%
	haloperidol	2	504	0.90	0.69, 1.18	0.440	0%
Muscle rigidity	risperidone	2	483	1.18	0.80, 1.74	0.390	0%
	placebo	2	827	2.52	0.23, 27.02	0.450	56%
Salivary hypersecretion	risperidone	2	483	1.23	0.82, 1.85	0.320	0%
	haloperidol	2	504	0.45	0.13, 1.56	0.210	67%
	placebo	2	827	1.44	0.30, 6.90	0.650	0%
Tremor[a]	risperidone/paliperidone	3	652	0.09	-0.17, 0.35	0.490	97%
	haloperidol	2	504	-0.16	-0.24, -0.08	<0.001	0%
	placebo	3	836	0.03	-0.05, 0.12	0.430	75%
Weight increase	risperidone	2	483	-0.04	-0.07, -0.01	0.010	0%
	aripiprazole	2	211	0.01	-0.13, 0.15	0.900	54%

[a] effect size RD was used due to zero event exis
RR, risk ratio; RD, risk difference.

The effects of blonanserin may be further attributed to its selective antagonism of dopamine D3 and serotonin 5-HT2A. In this study, blonanserin-induced negative symptoms were significantly improved compared with haloperidol, possibly due to the selective antagonism of dopamine D3 and 5-HT2A from blonanserin. Unlike other drugs, blonanserin is a complete antagonist of D3 receptors and binds to them with higher affinity than risperidone, olanzapine and aripiprazole in humans (35,36). Animal trials suggest that D3 receptor antagonism may be beneficial for the functioning of the frontal cortex, such as schizophrenia-associated negative symptoms and cognitive impairment, and may act on the reward system to enhance motivation. Moreover, alleviated negative symptoms are associated with improved social functioning, which is associated with enhanced intrinsic motivation or activation of the reward system (37,38). Therefore, the selective antagonism of D3 receptors of blonanserin improves social functioning by enhancing motivation and reducing negative symptoms, thereby contributing to the recovery of patients. We explore the differences between the efficacy and safety of these drugs and provide strong evidence for clinical decision-making.

However, this study has some limitations, as follows: 1) The included clinical studies mainly targeted Japan, Korea and China, with a lack of findings from non-Asian populations, posing certain limits in extrapolating results across the whole population. 2) The duration of intervention in these studies was mostly 6–8 weeks, and schizophrenia is a disorder requiring long-term medication, leading to inadequate long-term efficacy and safety data. 3) Despite the inclusion of 13 prospective studies in this study, only a small number of studies were included in the subgroup analysis with different controls, and the small sample size may have led to reduced statistical effectiveness. 4) Additional subgroup analysis of study duration, which may have effects on the blonanserin, is unavailable due to the limited number of publications in different control groups.

In conclusion, this study reveals that blonanserin exhibits efficacy comparable with risperidone/paliperidone and aripiprazole in treating schizophrenia; it is more effective than haloperidol to some extent and has satisfactory safety. However, the findings should be interpreted with caution due to certain limitations, with more studies required to further investigate the differences with other antipsychotic drugs.

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