Efficacy and safety of lurasidone for schizophrenia: A systematic review and meta-analysis of eight short-term, randomized, double-blind, placebo-controlled clinical trials

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Abstract. Lurasidone is an atypical anti-psychotic approved by the US Food and Drug Administration. It is mainly used to treat schizophrenia in adults through its antagonistic action on dopamine and 5-hydroxytryptamine receptors. The present study systematically assessed the efficacy and safety of lurasidone in the treatment of schizophrenia. Clinical, double-blind, parallel, randomized controlled trials (RCTs) of lurasidone in the treatment of schizophrenia were retrieved from PubMed\Medline, EBSCO, Embase, Cochrane Library, OVID, Web of Science and related clinical trial registration websites up to May 2023. A total of two investigators independently screened the included references and evaluated their quality. RevMan 5.3 software was used for meta-analysis of each measure outcome. The present systematic review was registered in PROSPERO (ID=CRD42018108178). A total of eight RCTs were included in the present study, including a total of 2,456 patients with schizophrenia. All eight references were randomized, double-blind and parallel control trials. All eight references were evaluated as high quality. The meta-analysis results demonstrated that there were no significant change in total Positive and Negative Syndrome Scale (PANSS) score, Clinical Global Impression of Severity (CGI-S) score and Montgomery-Asberg Depression Rating Scale (MADRS) between the 40 mg lurasidone group and the placebo group (P>0.05). However, as the dosage increased, the 80, 120 and 160 mg lurasidone groups had significant changes in total PANSS score, CGI-S score and MADRS Compared with placebo (P<0.05), although changes in MADRS in the 120 mg lurasidone group were not statistically significant (P>0.05). In terms of safety, the changes in the incidence of agitation in the 40 mg lurasidone group (P<0.05), vomiting in the 80 mg group (P<0.05) and akathisia in the 160 mg group (P<0.05) were statistically significant and there were also statistically significant changes in the incidence of akathisia, nausea, somnolence and extrapyramidal disorder among the 40, 80 and 120 mg lurasidone groups (P<0.05); No statistically significant changes in the in the incidence of other adverse reactions (P>0.05). In conclusion, existing evidence suggests that the initial dose of lurasidone for schizophrenia can be adjusted to 80 mg. As the condition aggravates, the dose can be incrementally increased to 160 mg. A dose of 160 mg lurasidone is recommended as the most efficacious and safe dose for acute schizophrenia and the risk of occurrence of akathisia, nausea, somnolence and extrapyramidal disorder is still high when lurasidone is administered at a dose of 80-120 mg. The dose should be promptly adjusted or the drug should be withdrawn if the aforementioned adverse reactions worsen. Multi-center, high-quality and long-term clinical RCTs influenced by the included references are still necessary to support the aforementioned conclusions.

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Introduction

In recent years, mental illness has become one of the major diseases seriously threatening human health. It is estimated that 45-50 million individuals (1%) are suffering from schizophrenia worldwide, 33 million of whom are from developing countries (1,2). As a common mental illness, schizophrenia can be found in various social cultures and geographic regions, and its incidence and prevalence are roughly the same all over the world. Its life-time prevalence rate is ~1% (3-5). Clinical symptoms of schizophrenia are complex and diverse. Clinical features vary among different individuals, disease types and stages (6). The etiology of schizophrenia has not yet been fully elucidated. However, in terms of behavior, the majority of patients exhibit perceptive, thinking, emotional, volitional and behavioral disorders (7-10). At present, drug therapy is a major option for schizophrenia. Since the advent of chlorpromazine in 1952, antipsychotics have been developed for more than 60 years. Great progress has been made in their research,

and a large number of novel anti-psychotics have entered into different phases of clinical trials. Atypical antipsychotics have become the first-line medication for schizophrenia due to their outstanding efficacy and safety (11). Lurasidone (trade name, Latuda™), a novel atypical antipsychotic, was approved by the FDA on October 28, 2010. It mainly functions through the complete antagonistic action on dopamine D_2 and 5-hydroxytryptamine$_{2A}$ $(5\text{-HT})_{2A}$ receptors (12), and is another novel antipsychotic after iloperidone and asenapine (13). One study showed lurasidone is safe in treating schizophrenia, making it a compelling option for patients with schizophrenia (14). Lurasidone greatly enhances patient compliance and its clinical application rate is increasing due to its oral, once-daily administration mode. However, there are some inconsistent conclusions of efficacy and tolerability of lurasidone in treating schizophrenia. A network meta-analysis suggested that lurasidone 80 mg/day decreases body weight. Conversely, lurasidone 40 mg/day was associated with weight increase (15). A meta-analysis found that lurasidone reduced most psychopathology symptoms, but it did not analyze the PANSS score, CGI-S score and MADRS which can be useful for the clinicians (16). Therefore, studies of re-evaluation of the post-marketing efficacy and safety of lurasidone are receiving growing attention from clinicians and pharmacists. By searching a large amount of bibliographic databases, a number of RCTs regarding the clinical efficacy and safety of lurasidone in schizophrenia were identified; however, the efficacy and safety caused by dosage discrepancies were also prominent. The aim of the present systematic review was to ascertain the efficacy and safety of different doses of lurasidone in schizophrenia using evidence-based medicine methods and strict quality standards for the included references (17), providing an evidence-based basis for the clinical application of this drug.

Materials and methods

Methods. The present study was conducted and reported according to The Cochrane Collaboration's recommendations and guidelines for conducting systematic reviews and meta-analyses for observational studies (18,19), as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (20,21) statement.

Study eligibility criteria. The *a priori* inclusion criteria for the present meta-analysis included: i) Double-blind, parallel-controlled, randomized clinical trials; ii) included patients of any age or disease severity [meeting criteria for the diagnosis of acute or chronic schizophrenia, psychosis, schizoaffective disorder, schizophreniform disorder and other psychotic disorders as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (22), DSM-IV Text Revision (23) and International Classification of Diseases, Tenth Revision Classification of Mental and Behavioral Disorders (24-26)]; iii) relevant interventions assigned to lurasidone 40, 80, 120 and 160 mg/day were selected for primary comparison compared with placebo independently; iv) the primary efficacy outcome measure was a change from baseline in the Positive and Negative Syndrome Scale (PANSS) (27), Clinical Global Impression of Severity (CGI-S) (28) and Montgomery-Asberg Depression Rating Scale (MADRS) (29); and v) the safety outcome was the rate of discontinuation due to adverse effects (>5%). Exclusion criteria included the following: i) Systematic reviews; ii) review article; iii) case-control study designs; iv) animal studies; v) comment; vi) incomplete data; vii) case reports; viii) improper statistical method; and, ix) duplicate publications.

Data sources and search strategy. PubMed\Medline (https://pubmed. ncbi.nlm.nih.gov), EBSCO (https://search.ebscohost.com), Embase (https://www.em-base.com), Cochrane library (https://www.cochranelibrary.com/?content-Language=eng), OVID (https://ovidsp.ovid.com) and Web of Science (https://www.webofscience.com/wos) were searched up to May 2023. No limits were placed on this search and there were no language restrictions. Potentially relevant unpublished data were searched using ClinicalTrials.gov (Drugs@FDA; https://www.accessdata.fda.gov/), the Chinese Clinical Trial Registry (http://www.chictr.org.cn/), European Union Drug Regulating Authorities Clinical Trials (https://eudract.ema.europa.eu/index.html), and the World Health Organization International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/). Reference lists of included and excluded articles were searched for randomized clinical trials matching the inclusion criteria. The search was performed using the terms: 'lurasidone', 'Latuda', 'Latuda', 'lurasidone hydrochloride', 'placebo', 'schizophrenia', 'schizoaffective disorder', 'schizophreniform disorder', 'efficacy', 'safety', 'tolerability', 'Clinical trial', 'randomized controlled trial', 'RCT', 'double-blind' and 'parallel-controlled'. The PubMed search string used was as follows: '(lurasidone OR Latuda OR lurasidone hydrochloride) AND (placebo) AND (schizophrenia OR schizoaffective disorder OR schizophreniform disorder OR) AND (efficacy) AND (safety OR tolerability) AND (Clinical trial OR randomized controlled trial OR RCT) AND (double-blind) AND (parallel-controlled)' AND (human OR humans).

Study selection. Each search was conducted separately and then downloaded as a separate file. In order to minimize selection bias, two researchers (SG and LF) independently screened the titles, abstracts, full-texts and extracted data based on the pre-defined eligibility criteria, and evaluated the quality of the literatures. If they had a disagreement, a third researcher was used to solve the disagreement when necessary.

Data extraction. For each study, two researchers extracted information on study characteristics, baseline characteristics of patients such as age, duration of illness, duration of treatment, PANSS total score and CGI-severity score, MADRS total score, ethnicity, study location, interventions of the trial, end points such as primary efficacy outcomes (PANSS total score change, CGI-S score change and MADRS total score change) and safety outcomes (adverse effects).

Quality assessment. The quality of literature was assessed using the Cochrane system evaluation (version 5.1.0) RCTs bias risk assessment tool (30). The predefined key domains included random sequence generation, allocation concealment, blinding, incomplete outcome data addressed,

intention-to-treat analysis, free of selective reporting and free of other bias. Each item was classified as 'yes' (low risk of bias), 'no' (high risk of bias) or 'unclear'.

Statistical analysis. All outcomes were pooled using RevMan 5.3 software (download from http://www.cochrane.org/). Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes (such as response rates) and the standardized mean difference (SMD) was used to report continuous outcomes (such as scale scores). The I^2 statistic was calculated to estimate heterogeneity. If I^2 was ≤50%, the fixed-effects model with the Mantel-Haenszel (M-H) method was selected; otherwise, the random-effect model (REM) was adopted. The risk of publication bias was shown as a funnel plot. P<0.05 was considered to indicate a statistically significant difference.

Results

Literature search and study characteristics. The search yielded 744 citations, of which eight articles (2,456 patients) met the inclusion criteria (31-38). A total of five articles defined response using the PANNS total score change and CGI-S score change (32-35,37) and three articles defined response using the MADRS total score change (34,35,37) in the lurasidone (40 mg/day) group compared with placebo group. A total of five articles defined response using the PANNS total score change and CGI-S score change (31,33,35-37) and four articles defined response using the MADRS total score change (31,35-37) in the lurasidone (80 mg/day) group compared with placebo group. A total of three articles defined response using the PANNS total score change and CGI-S score change (32,34,35), and two articles defined response using the MADRS total score change (34,35) in the lurasidone (120 mg/day) group compared with placebo group. One article defined response using the PANNS total score change, CGI-S score change and MADRS total score change in the lurasidone (160 mg/day) group compared with placebo group (31). A total of eight articles defined response using the safety of different doses of lurasidone compared with placebo (31-38). A total of eight articles were published in public databases. The eight articles were conducted in 14 different countries (United States, Ukraine, Russia, Bulgaria, Romania, Colombia, Mexico, Poland, Philippines, South Korea, Malaysia, Spain, France and Hungary). A total of five articles were multicenter clinical studies in the United States (32,35-38). A total of three articles were multi-country, multi-center clinical studies (31,33,34). The flow diagram in Fig. 1 shows additional details regarding trial selection and Table I shows the characteristics of the included studies. A total of eight articles were of a double-blind parallel-controlled design (Yes) (31-38). For all eight articles, it was not clear if these were selective reports (31-38). One article was relatively vague on the other bias (No) (36). Details of the risk of bias assessment are shown in Fig. 2.

Primary efficacy outcomes. Articles used the PANSS, CGI-S and MADRS scale to measure the efficacy of lurasidone. A total of seven articles reported the response using the PANSS, CGI-S or MADRS scale at six weeks. Patients were considered to be PANSS, CGI-S and MADRS scale responders if they achieved a decrease in their total score from baseline at the end of the study.

Lurasidone (40 mg/day). There were no statistically significantly changes associated with PANSS total score change (P>0.05; SMD, -2.57; 95% CI, -5.19 to 0.06; I^2, 99%), CGI-S score change (P>0.05; SMD, 1.64; 95% CI, -1.88 to 5.15; I^2, 100%) or MADRS total score change (P>0.05; SMD, -1.53; 95% CI, -4.02 to 0.97; I^2, 99%) in the lurasidone (40 mg/day) group compared with the placebo group (Table II).

Lurasidone (80 mg/day). There were statistically significant changes on PANSS total score change (P<0.05; SMD, -3.90; 95% CI, -5.94 to -1.86; I^2, 99%), CGI-S score change (P<0.05; SMD, -3.78; 95% CI, -5.46 to -2.10; I^2, 99%) or MADRS total score change (P<0.05; SMD, -2.90; 95% CI, -4.79 to -1.02; I^2, 99%) in the lurasidone (80 mg/day) group compared with the placebo group (Table II).

Lurasidone (120 mg/day). With the exception that there was no statistical difference in MADRS total score change (P>0.05), lurasidone (120 mg) had a statistically significant superior effect on PANSS total score change (P<0.05; SMD, -3.15; 95% CI, -4.49 to -1.81; I^2, 96%) or CGI-S score change (P<0.05; SMD, -3.86; 95% CI, -5.55 to -2.17; I^2, 98%) in the lurasidone (120 mg/day) group compared with the placebo group (Table II).

Lurasidone (160 mg/day). There were statistically significant changes on PANSS total score change (P<0.05; SMD, -9.69; 95% CI, -10.61 to -8.77), CGI-S score change (P<0.05; SMD, -7.79; 95% CI, -8.74 to -7.21) or MADRS total score change (P<0.05; SMD, -6.78; 95% CI, -7.44 to -6.12) in the lurasidone (1,600 mg/day) group compared with the placebo group (Table II).

Safety outcomes. In terms of safety, a parallel, independent meta-analysis of 11 adverse reactions with a rate of >5% in eight articles, including headache, insomnia, akathisia, nausea, vomiting, anxiety, somnolence, agitation, dyspepsia, constipation and extrapyramidal disorder was conducted. The results of the meta-analysis of adverse reactions showed that, compared with the placebo group, i) The incidence of akathisia (response rate; M-H RR, 3.66; 95% CI, 2.07 to 6.47), nausea (response rate; M-H RR, 2.00; 95% CI, 1.28 to 3.13), somnolence (response rate; M-H RR, 1.82; 95% CI, 1.12 to 2.95), agitation (response rate; M-H RR, 2.09; 95% CI, 1.17 to 3.73) and extrapyramidal disorder (response rate; M-H RR, 2.8; 95% CI, 1.55 to 5.06) was higher in the lurasidone (40 mg/day) group (Table III); ii) the incidence of akathisia (response rate; M-H RR, 3.56; 95% CI, 2.15 to 5.88), nausea (response rate; M-H RR, 2.38; 95% CI, 1.58 to 3.59), vomiting (response rate; M-H RR, 2.06; 95% CI, 1.28 to 3.30), somnolence (response rate; M-H RR, 2.05; 95% CI, 1.29 to 3.28) and extrapyramidal disorder (response rate; M-H RR, 2.36; 95% CI, 1.11 to 5.04) was higher in the lurasidone (80 mg/day) group (Table III); iii) the incidence of akathisia (response rate; M-H RR, 11.86; 95% CI, 5.03 to 27.94), nausea (response rate; M-H RR, 2.21; 95% CI, 1.25 to 3.90), somnolence (response rate; M-H RR, 2.95; 95% CI, 1.64 to 5.29) and extrapyramidal disorder (response rate; M-H RR, 5.18; 95% CI, 2.62 to 10.52) was higher in the lurasidone (120 mg/day) group (Table III); and iv) the incidence of akathisia (response rate; M-H RR, 6.32; 95% CI, 1.61 to 24.83) was higher in the lurasidone (160 mg/day) group (Table III).

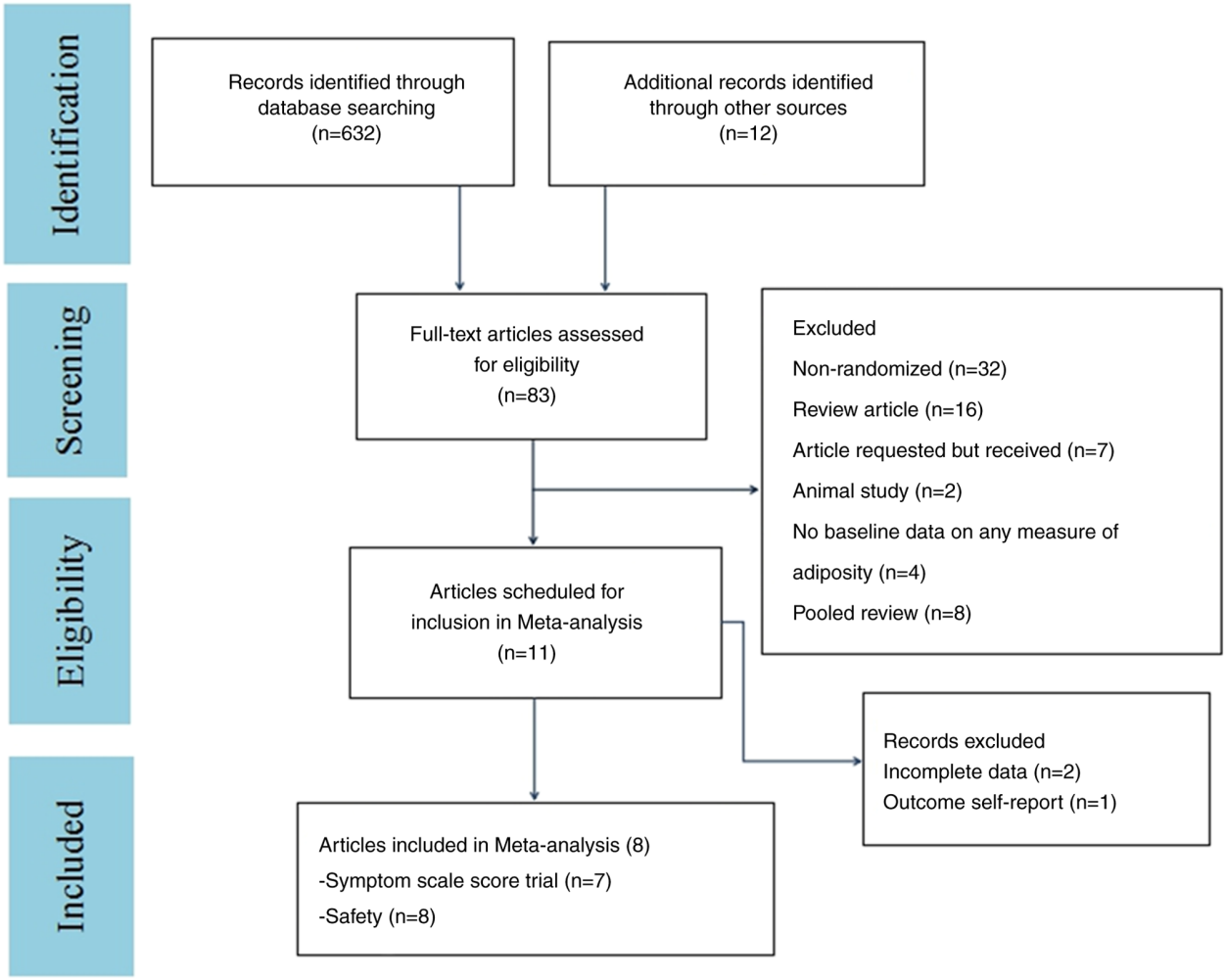

Figure 1. PRISMA flowchart of study selection.

Discussion

Lurasidone is a benzothiazole atypical antipsychotic. The US FDA has recommended an initial dose of 40 mg/day, which can be increased to 80 mg/day (39,40). Lurasidone has been approved to treat the patients with schizophrenia in the Canada, USA, Europe and Australia (41,42). Lurasidone has a potent binding affinity for dopamine D2, 5-hydroxytryptamine (5-HT)2A, 5-HT7, 5-HT1A and noradrenaline α2C receptors (43), which make lurasidone be reduction in negative symptoms, improvement in cognition and circadian rhythm regulation, improvement in depressive symptoms, reduced drowsiness and somnolence (44,45). Compared with other second generation antipsychotics, lurasidone has affinity for to muscarinic M1 receptors and histamine H1 receptors, both of which can make lurasidone exert weight gain, impaired glucose metabolism and increased plasma lipid levels caused by other antipsychotics (43). A meta-analysis also concluded that lurasidone had the lowest risk of weight gain and glucose changes compared with other antipsychotics (46). Lurasidone offers an obvious advantage to patients as it has promising effects on glucose and lipid parameters and body weight (40,47), which make lurasidone a good choice for clinicians and patients. A review concluded that clinical trials showed the effectiveness of lurasidone is very promising in treating these disorders such as bipolar depression disorder (48). Some clinical trials show that lurasidone is an effective treatment option for patients with schizophrenia (49,50). Miura *et al* (51) noted that lurasidone improves functional and cognitive behaviors of patients with schizophrenia, especially in long-term treatment. Patients with schizophrenia can use the antipsychotics to prevent schizophrenia in the long-term treatment. Most adverse reactions of lurasidone are only mild to moderate (49,50), and lurasidone is found to cause less weight gain but higher rates of extrapyramidal side-effects, anxiety and akathisia compared with olanzapine (35). Compared with quetiapine, lurasidone also shows a higher incidence of extrapyramidal side-effects (37). A study reported that lurasidone had no difference in adverse effects in patients with schizophrenia, besides lower rates of somnolence compared with ziprasidone (52). Lurasidone has aroused the attention of clinicians and pharmacists as an effective and safe treatment for patients (48). A meta-analysis concluded that lurasidone was superior to placebo in total psychopathology, positive symptoms or negative symptoms (49). However, the present study did not include the efficacy outcome measures, such as total PANSS score, which can more useful the clinicians (53). Therefore, the present study analyzed the outcome measures of total PANSS score,

Table I. Basic characteristics of literatures (mean ± standard deviation).

First author/s, year	Interventions	Patients (n)	Age (years)	Duration of illness (years)	Treatment duration (weeks)	PANSS total score	CGI-severity score	MADRS total score	Ethnicity	Outcome	(Refs.)
Goldman, *et al*, 2017	Lu 40 mg Lu 80 mg Placebo	108 106 112	15.5±1.3 15.3±1.4 15.3±1.4	Not reported	6	94.5±11.0 94.0±11.1 92.8±11.1	4.9±0.6 4.8±0.7 4.6±0.7	Not reported	White, Black, Asian, Other	①②③④	(33)
Loebel, *et al*, 2013	Lu 80 mg Lu 160 mg Placebo	125 121 121	36.2±10.9 37.9±11.3 37.4±10.8	11.1±9.2 11.8±8.8 11.3±9.3	6	97.7±9.7 97.5±11.8 96.6±10.2	5.0±0.5 5.0±0.6 4.9±0.5	11.6±7.6 11.2±7.8 11.3±6.7	White, Black, Asian, Other	①②③④	(31)
Loebel, *et al*, 2016	Lu 80 mg Lu 160 mg Placebo	52 43 112	42.0±10.9 41.3±9.0 40.7±11.6	Not reported	6	93.3±9.4 96.0±9.6 97.8±10.3	4.9±0.5 5.0±0.6 4.9±0.6	Not reported	White, Black, Asian, Other	④	(38)
Meltzer, *et al*, 2011	Lu 40 mg Lu 120 mg Placebo	119 118 114	37.7±11.0 37.9±11.2 37.0±11.3	13.3±9.9 14.7±11.0 12.6±9.6	6	96.6±10.7 97.9±11.3 95.8±10.8	5.0±0.7 5.0±0.6 4.9±0.7	10.8±7.0 14.4±7.2 10.6±6.1	White, Black, Asian, Other	①②③④	(34)
Nakamura, *et al*, 2009	Lu 80 mg Placebo	90 90	39.7±9.9 41.9±9.8	Not reported	6	94.4±10.9 96.0±11.6	4.8±0.7 4.8±0.7	14.2±8.0 14.5±8.3	White, Black, Other	①②③④	(36)
Nasrallah, *et al*, 2013	Lu 40 mg Lu 80 mg Lu 120 mg Placebo	122 119 124 124	40.3±11.3 38.6±9.6 37.6±11.1 38.2 9.9	Not reported	6	96.5±11.5 96.0±10.8 96.0±9.7 96.8±11.1	5.0±0.7 4.9±0.6 4.9±0.6 4.9±0.6	11.2±6.4 11.1±7.1 11.3±7.3 11.9±6.8	White, Black, Asian, Other	①②③④	(35)
Ogasa, *et al*, 2013	Lu 40 mg Lu 120 mg Placebo	108 106 112	39.8±9.5 41.0±9.0 38.1±9.7	Not reported	6	92.8±16.1 89.6±13.4 93.3±16.4	4.8 0.7 4.7±0.6 4.6±0.7	Not reported	White, Black, Other	①②③④	(32)
Potkin, *et al*, 2015	Lu 40 mg Lu 80 mg Placebo	67 71 72	42.0±10.9 42.2±8.3 41.0±9.7	Not Reported	6	93.4±15.0 93.1±13.6 96.5±15.2	4.8±0.8 4.7±0.8 4.8±0.7	13.1±7.5 13.6±8.0 14.7±8.6	White, Black, Asian, Other	①②③④	(37)

① PANSS, Positive and Negative Syndrome Scale; ② CGI-S, Clinical Global Impression of Severity; ③ MADRS, Montgomery-Asberg Depression Rating Scale; ④ Safety; Lu, lurasidone.

Table II. Comparison of therapeutic effect analysis in each trial group.

Therapeutic effect analysis	Lurasidone 40 mg	Lurasidone 80 mg	Lurasidone 120 mg	lurasidone 160 mg
PANNS total score change	-2.57 (-5.19 to 0.06) Z=1.92 (P=0.06) 5 trials	-3.90 (-5.94 to -1.86)[a] Z=3.75 (P=0.0002) 5 trials	-3.15 (-4.49 to -1.81)[a] Z=4.61 (P<0.00001) 5 trials	-9.69 (-10.61 to -8.77)[a] Z=20.69 (P<0.00001) 1 trial
CGI-S score change	1.64 (-1.88 to 5.15) Z=0.91 (P=0.36) 5 trials	-3.78 (-5.46 to -2.10)[a] Z=4.41 (P<0.0001) 5 trials	-3.86 (-5.55 to -2.17)[a] Z=4.47 (P<0.00001) 5 trials	-7.97 (-8.74 to -7.21)[a] Z=4.47 (P<0.00001) 5 trials
MADRS total score change	-1.53 (-4.02 to 0.97) Z=1.20 (P=0.23) 3 trials	-2.90 (-4.79 to -1.02)[a] Z=3.02 (P=0.003) 4 trial	0.17 (-1.46 to 1.79) Z=0.20 (P=0.84) 2 trials	-6.78 (-7.44 to -6.12) Z=0.20 (P=0.84) 1 trial

[a]P<0.05.

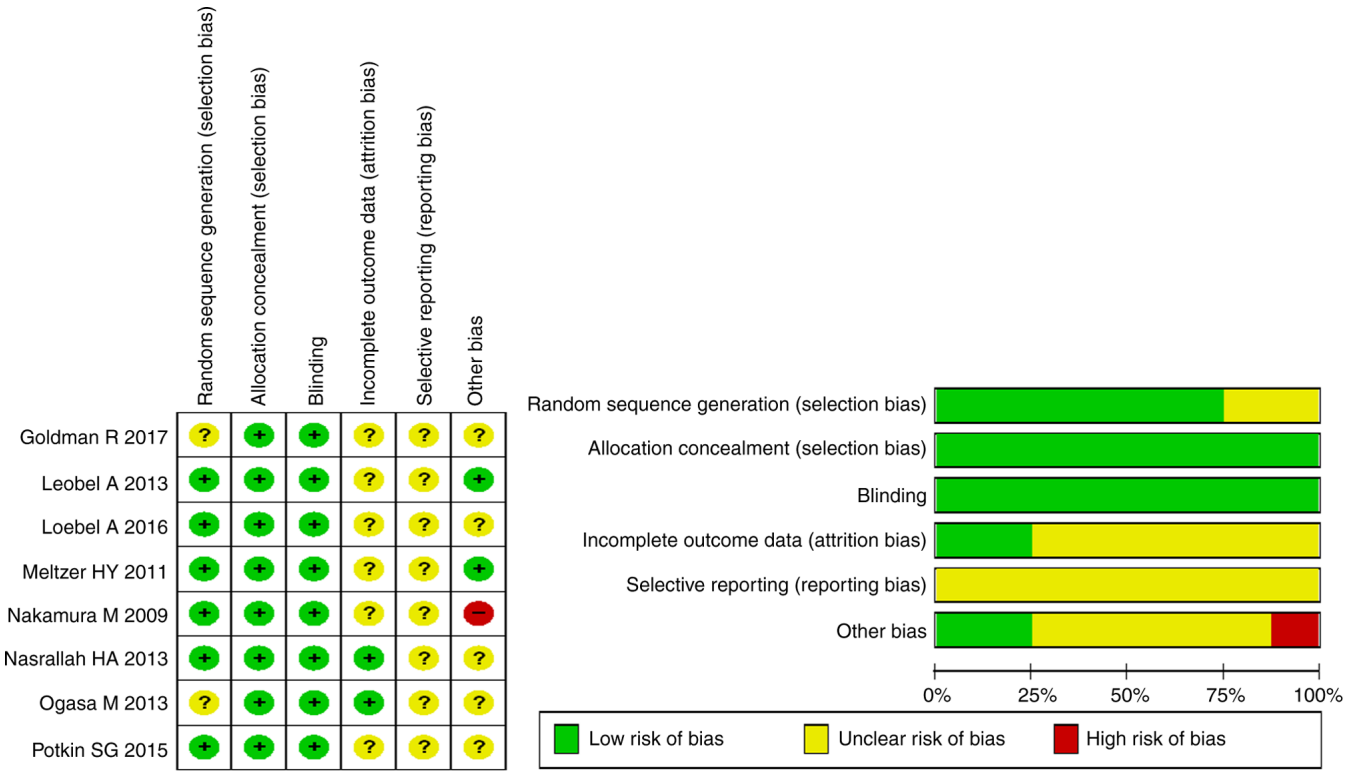

Figure 2. Cochrane risk of bias assessment.

CGI-S score and total MADRS score and included more safety outcome measures, which can provide more suggestions to clinicians on the choice of drug. Moreover, a randomized trial reported that lurasidone 80 mg is not effective in the treatment in schizophrenia (37). However, another trial reported that lurasidone 80 mg was superior than a placebo (35). Other trials showed significant symptom improvement in the PANSS total score with schizophrenia in the lurasidone 40 and 80 mg (49). This inconsistency confused the psychiatrist and patients about whether lurasidone 80 mg can be used to treat patients with schizophrenia. The results of the present study analyzed the efficacy and safety of all the doses of lurasidone in the treatment of patients with schizophrenia and, given the suggestion of the dose choice, will help clinicians make a clinical decision on the dose of lurasidone.

The present systematic review and eight articles were selected according to the inclusion and exclusion criteria involving short-term (6-week) clinical RCTs of the efficacy and safety of lurasidone in treatment of schizophrenia (31-38). All eight articles were double-blind, parallel control trials with a low risk of publication bias. A subgroup analysis of changes in total PANSS score, CGI-S score and total MADRS score was conducted to evaluate differences in clinical symptom improvement and adverse reactions between each experimental group (40, 80, 120 and 160 mg lurasidone) and the control group. In terms of

Table III. Absolute risk ratio of adverse reactions for lurasidone compared with placebo.

Adverse reaction	Headache	Insomnia	Akathisia	Nausea	Vomiting	Anxiety	Somnolence	Agitation	Dyspepsia	Constipation	Extrapyramidal disorder
Lurasidone 40 mg	1.00% (0.73-1.37%) I^2=13% 5 trials	1.01% (0.65-1.56%) I^2=0% 5 trials	3.66% (2.07-6.47%)[a] I^2=38% 5 trials	2.00% (1.28-3.13%)[a] I^2=19% 5 trials	1.24% (0.72-2.12%) I^2=14% 5 trials	1.35% (0.74-2.46%) I^2=0% 2 trials	1.82% (1.12-2.95%)[a] I^2=0% 5 trials	2.09% (1.17-3.73%)[a] I^2=0% 4 trial	0.98% (0.59-1.63%) I^2=0% 4 trial	0.66% (0.19-2.30%) I^2=53% 3 trials	2.8% (1.55-5.06%)[a] I^2=0% 5 trials
Lurasidone 80 mg	0.85% (0.64-1.14%) I^2=0% 6 trials	0.94% (0.64-1.36%) I^2=27% 6 trials	3.56% (2.15-5.88%)[a] I^2=0% 6 trials	2.38% (1.58-3.59%)[a] I^2=38% 6 trials	2.06% (1.28-3.30%)[a] I^2=0% 6 trials	0.76% (0.24-2.39%) I^2=54% 4 trial	2.05% (1.29-3.28%)[a] I^2=0% 6 trials	0.76% (0.43-1.33%) I^2=0% 5 trials	1.38% (0.81-2.34%) I^2=0% 4 trial	1.12% (0.60-2.10%) I^2=12% 3 trials	2.36% (1.11-5.04%)[a] I^2=0% 4 trial
Lurasidone 120 mg	0.90% (0.63-1.30%) I^2=0% 3 trials	1.04% (0.61-1.79%) I^2=39% 3 trials	11.86% (5.03-27.94%)[a] I^2=0% 3 trials	2.21% (1.25-3.90%)[a] I^2=0% 3 trials	1.63% (0.90-2.98%) I^2=0% 3 trials	1.47% (0.63-3.47%) 1 trial	2.95% (1.64-5.29%)[a] I^2=0% 3 trials	1.75% (0.75-4.08%) I^2=30% 2 trials	1.22% (0.68-2.20%) I^2=47% 3 trials	0.70% (0.08-6.13%) I^2=55% 2 trials	5.18% (2.62-10.52%)[a] I^2=0% 3 trials
Lurasidone 160 mg	0.94% (0.49-1.78%) I^2=0% 2 trials	0.63% (0.34-1.17%) I^2=0% 2 trials	6.32% (1.61-24.83%)[a] I^2=0% 2 trials	1.75% (0.67-4.55%) I^2=0% 2 trials	1.81% (0.74-4.46%) I^2=0% 2 trials	0.76% (0.21-2.79%) I^2=60% 2 trials	2.38% (0.26-22.12%) I^2=67% 2 trials	0.55% (0.24-1.25%) I^2=30% 2 trials	1.75% (0.53-5.82%) 1 trial	0.33% (0.04-3.16%) 1 trial	1.04% (0.21-5.17%) 1 trial

[a]P<0.05.

efficacy evaluation, the results demonstrated that there were no significant change in total PANSS score, CGI-S score and MADRS between the 40 mg lurasidone group and the placebo group (P>0.05). The 80, 120 and 160 mg lurasidone groups had significant changes in total PANSS score, CGI-S score and MADRS compared with a placebo (P<0.05), although changes in MADRS in the 120 mg lurasidone group were not statistically significant (P>0.05). The results demonstrated that the clinical symptoms of patients with schizophrenia did not significantly improve when an initial dose (40 mg) of lurasidone was administered. However, as the dose increased to 80-160 mg, clinical symptom scores in enrolled patients significantly changed compared with the placebo group. This conclusion suggests that clinicians should choose lurasidone 80 mg/day in the treatment of schizophrenia as the initial dose. The recommend initial dose of lurasidone by FDA is 40 mg/day (12). However, the present authors recommend lurasidone 80 mg/day as the initial dose because the lurasidone 40 mg/day did not significantly improve the clinical symptoms of schizophrenia, which is different from the previous conclusions. In terms of safety assessment, combined meta-analyses were independently conducted on 11 adverse reactions (headache, insomnia, akathisia, nausea, vomiting, anxiety, somnolence, agitation, dyspepsia, constipation and extrapyramidal disorder) with an incidence of >5% in the eight included references. Akathisia, nausea, somnolence and extrapyramidal disorder occurred significantly more frequently in each experimental dose group (40, 80, 120 and 160 mg lurasidone) compared with the placebo group. As for the relationship between adverse reactions and the dose increase of lurasidone, there was no linear relationship observed in the present systematic review. The results showed that the changes in the incidence of agitation in the 40 mg lurasidone group (P<0.05), vomiting in the 80 mg group (P<0.05) and akathisia in the 160 mg group (P<0.05) were statistically significant and there were also statistically significant changes in the incidence of akathisia, nausea, somnolence and extrapyramidal disorder among the 40, 80, 120 mg lurasidone groups (P<0.05); The incidence of other adverse reactions was statistically insignificant (P>0.05) as the dose of lurasidone increased to 160 mg, except for the incidence of akathisia, which was statistically significant (P<0.05). A dose of 160 mg lurasidone can be safer than other doses as the incidence of adverse reactions in 160 mg lurasidone was not statistically significant except for the incidence of akathisia. Therefore, 80, 120 and 160 mg lurasidone can be chosen as the treatment dose because of their outstanding efficacy and safety. The present study showed that 160 mg lurasidone is the most effective with the least adverse effects compared with other doses and when clinicians choose the 80 or 120 mg lurasidone as the treatment dose, the risk of occurrence of akathisia, nausea, somnolence and extrapyramidal disorder should be noticed and 80 mg lurasidone should be the initial dose rather than 40 mg. These conclusions are different from other studies which conclude that 40 mg lurasidone is effective in the treatment of schizophrenia (12,16,52). The different dose choice suggestions should be helpful to guide the dose adjustment of lurasidone for schizophrenia. However, these results were influenced by the bibliographic bias and the integrity of the results and data. More high-quality clinical studies are necessary for verification.

Although the eight references included in the present review were strictly screened on the basis of the inclusion and exclusion criteria, with rigorous and standardized quality evaluation, shortcomings remained in the systematic review and the meta-analysis of measure outcomes. First, there might be a risk of bibliographic selection bias in the bibliographic screening because two investigators independently read and reviewed references in parallel on the basis of the inclusion and exclusion criteria. The risk of literature selection bias during the screening of reference material could not be excluded. Second, some grey-literature and non-traditional sources of evidence depending on whether there was a confidentiality agreement were unable to properly supply the inclusion data such as CGI-S score. Therefore, the data included in the analysis might show some degree of publication bias. Third, in the eight references included in the analysis (31-38), fundamental features such as age, underlying diseases, previous treatment conditions, BMIs and body weights of patients enrolled were not strictly screened. There were only two studies (31,34) that provided the duration of disease (course of disease) and there were three studies (32,33,38) that did not provide baseline levels of the MADRS score. Fourth, due to the fact that the eight references (31-38) included in the analysis were in English, rather than other languages, there might be a risk of language bias. It was considered that scientific and complete results could be assured by strict screening and careful quality assessment of the references, as well as use of proper methods, which means the results are of high value for clinical reference.

In conclusion, existing evidence suggests that the initial dose of lurasidone for schizophrenia can be adjusted to 80 mg and even incrementally to 160 mg as the disease aggravates. The dose of 160 mg lurasidone is recommended as the most efficacious and safe dose for acute schizophrenia. The risk of akathisia, nausea, somnolence and extrapyramidal disorder is still high when lurasidone is administered at a dose of 80-120 mg. The dose should be promptly adjusted or the drug should be withdrawn if the aforementioned adverse reactions worsen. Multi-center, high-quality and long-term clinical RCTs influenced by the included references are still necessary to support the aforementioned conclusions.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

SG, LF, XX and ZY were involved in the design of the study, collected the data, undertook the statistical analyses and drafted the manuscript. ZY and XX participated in the design of the study, performed the statistical analyses, helped to interpret data and drafted the manuscript. SG and LF participated in the design of the study and helped to draft the manuscript. SG and LF collected the data and helped to interpret data. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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