

Lurasidone Versus Quetiapine for Bipolar Depression in Adolescents and Young Adults: A Randomized Non- Inferiority Trial

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Research Article

Keywords: bipolar depression, adolescent and young adult, lurasidone, quetiapine, randomized controlled trial

Posted Date: October 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11023557/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background Treating bipolar depression in adolescents and young adults is challenging, and clinical trial evidence guiding its management—particularly in non-Western populations—remains limited. Although both lurasidone and quetiapine are used in this population, no head-to-head comparison has been conducted. This study therefore compared the efficacy and safety of the two agents in Chinese patients aged 14–24 years with bipolar depression.

Methods This was a single-center, open-label, randomized non-inferiority trial with flexible dosing. Sixty patients were randomly assigned to receive 8 weeks of treatment with either lurasidone or quetiapine. The primary outcome was the change from baseline in MADRS total score at week 8. Secondary outcomes included treatment response, remission, anxiety symptoms, social functioning, and safety outcomes. Fifty-five patients were included in the primary analysis.

Results Ultimately, 55 patients were included in the full analysis set. Both lurasidone and quetiapine significantly reduced MADRS total scores after 8 weeks of treatment. No significant between-group difference was observed in MADRS score changes at week 8 (mean difference = -4.38 , 95% CI $[-8.67, 2.24]$, $P = 0.098$) or at any follow-up time point, or in anxiety symptom improvement, social functioning, treatment response, or remission rates. Additional intention-to-treat and sensitivity analyses confirmed the robustness of the primary findings. The two drugs showed distinct adverse event profiles: lurasidone was associated with higher incidences of akathisia, parkinsonism, nausea, and anxiety, whereas quetiapine was associated with more frequent somnolence. No serious adverse events, clinically significant metabolic abnormalities, or manic switches occurred in either group, and suicide risk remained stable throughout the trial.

Conclusions Lurasidone demonstrated efficacy comparable to that of quetiapine in Chinese adolescents and young adults with bipolar depression, with a distinct tolerability profile characterized by a lower sedative burden but higher rates of akathisia and parkinsonism. Given its lower sedative burden, lurasidone may be particularly suitable for students and young patients in educational or occupational settings, although further study is warranted.

Trial registration Chinese Clinical Trial Registry (ChiCTR), ChiCTR2100049426. Registered 02 August 2021. Ethics approval number: 2021(55h)-202199FS-2.

Introduction

Bipolar disorder is a prevalent and debilitating mental disorder, affecting more than 1% of the global population [1]. Approximately half of the patients experience their initial symptoms during childhood or early adulthood, with a significant proportion presenting initially with depressive symptoms [2]. Treating bipolar depression in these age groups presents a substantial challenge in psychiatric clinical practice. Managing adolescent and young adults bipolar disorder typically requires a multidisciplinary approach,

including pharmacotherapy, psychotherapy, and social support [3]. At present, pharmacotherapy is considered the cornerstone of treatment for bipolar depression.

The FDA has approved two medications for the treatment of bipolar I depression in patients aged 10–17 years: the olanzapine-fluoxetine combination (OFC) and lurasidone [4]; quetiapine is commonly used off-label for this indication [5]. Lurasidone, a benzisothiazole derivative, acts as a full antagonist at D2, 5-HT_{2A}, and 5-HT₇ receptors and a partial agonist at 5-HT_{1A} receptors, underlying its atypical antipsychotic and antidepressant effects [6]. It exhibits high affinity for 5-HT₇ receptors among antipsychotics and minimal off-target activity at M1, H1, α 1, and α 2A receptors, which may reduce the risk of sedation, weight gain, and orthostatic hypotension [7].

According to the 2018 CANMAT/ISBD guidelines for bipolar disorder, lurasidone has been upgraded to a first-line treatment for acute bipolar depression (previously second-line in the 2013 version). First-line treatments for acute bipolar I depression include quetiapine (Level 1), lurasidone (Level 2), lithium (Level 2), and lamotrigine (Level 2) monotherapy. The FDA-approved recommended dose of lurasidone for bipolar I depression in pediatric patients is 20 to 80 mg/d. Quetiapine at doses of 150–300 mg/d is an effective and well-tolerated first-line treatment for bipolar depression [8]. Current consensus regarding the management of mania and unipolar depression is relatively well-established; however, treatment guidelines specifically for bipolar depression remain limited. Therefore, the development of effective interventions for bipolar depression is an urgent priority [1].

Growing evidence supports the use of lurasidone in treating adult bipolar depression, particularly in bipolar I depression. However, there is a lack of consensus on the optimal dosing regimen and standardized dosing recommendations for lurasidone in the treatment of bipolar depression. This highlights the current uncertainty regarding its optimal therapeutic regime [9]. A published network meta-analysis by Ostacher et al. indicated that lurasidone yields superior antidepressant efficacy relative to aripiprazole and ziprasidone [10], with a lower risk of weight gain compared with quetiapine and olanzapine, as well as a reduced incidence of somnolence versus quetiapine and ziprasidone. However, head-to-head clinical trials comparing the efficacy and safety of lurasidone and quetiapine in adolescents and young adults with bipolar depression remain scarce.

A randomized controlled trial by Diao et al. found that lurasidone and quetiapine showed comparable efficacy in the treatment of bipolar depression [11]. Lurasidone was superior in improving cognitive function and had a more favorable weight change profile. This study provided new evidence for the clinical use of lurasidone, particularly for cognitive improvement in young patients with bipolar depression. However, it found no significant between-group differences in reducing depressive symptom severity. The high dropout rate in this study requires cautious interpretation of the results. Furthermore, the lurasidone dose used in this study (60 to 120 mg/d) was outside the standard recommended dose range. A dose–response meta-analysis suggested that a daily dose of 40–60 mg of lurasidone provides optimal effects in reducing depression, improving anxiety and decreasing functional disability [12]. In

another randomized controlled study, the lurasidone group was divided into a high-dose group (80–120 mg/d) and a low-dose group (20–60 mg/d) [13].

Nevertheless, treatment recommendations for adolescent and young adult bipolar depression are largely extrapolated from Western clinical trials, and high-quality head-to-head evidence in East-Asian youth remains scarce. Given ethnic differences in drug metabolism, tolerability, and clinical response, we conducted a single-center, flexible-dose, randomized non-inferiority trial comparing lurasidone and quetiapine in Chinese adolescents and young adults with bipolar depression, hypothesizing that lurasidone would be non-inferior to quetiapine.

Method

Subjects

Inclusion criteria were as follows: (1) aged 14–24 years ; (2) diagnosed of bipolar depression according to DSM-5 criteria, with a current major depressive episode of at least 2 weeks' duration; (3) a Montgomery-Åsberg Depression Rating Scale (MADRS; range, 0–60; higher scores indicating more severe depressive symptoms) score of ≥ 22 and a Young Mania Rating Scale (range, 0–60; higher score indicates more severe manic symptoms) score of ≤ 12 . Patients were excluded if they met any of the following criteria: (1) lifetime history of schizophrenia or other psychotic disorder, substance use disorder, or any psychiatric disorder other than bipolar disorder; (2) a MADRS item 10 score ≥ 4 or evidence of imminent suicidal risk; (3) treatment with monoamine oxidase inhibitors (MAOIs), fluoxetine, clozapine, or any long-acting injectable depot antipsychotic within 21 days prior to screening; (4) any medical condition that could alter absorption, metabolism, or excretion of the study drug, or any contraindication to the study medications .

Study Design

This randomized, open-label, non-inferiority trial with flexible dosing was conducted at Beijing Anding Hospital, Capital Medical University, Beijing, China, and received approval from the local independent ethics committee. All participants or their legal guardians provided written informed consent prior to enrollment. This study adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. The study ethics approval number: 2021(55h)-202199FS-2, and the clinical trial registration number was ChiCTR2100049426.

Eligible patients who fulfilled the study criteria were randomly allocated in a 1:1 ratio to receive 8 weeks of treatment with lurasidone or quetiapine. Randomization was performed using a computer-generated block randomization method (block size of 4) by independent statisticians not involved in the study. To ensure allocation concealment, randomization codes were stored in opaque, sealed envelopes. In this trial, investigators and participants were unblinded to treatment assignment, whereas outcome raters remained blinded throughout the study.

For the lurasidone group, the dose was 10 mg/d on days 1–2, 20 mg/d on days 3–6, and 40 mg/d from day 7 onwards. For the quetiapine group, the dose was 50 mg/d on days 1–2, 200 mg/d on days 3–6, and 300 mg/d from day 7 onwards. In special circumstances, if a patient was unable to increase to the target dose due to tolerability issues, the titration speed and final dosage were to be adjusted as appropriate.

Concomitant Medications

During the study, concomitant use of anti-Parkinson agents, anxiolytics, and hypnotics (e.g., trihexyphenidyl, lorazepam, zopiclone, zolpidem, eszopiclone, zaleplon) was permitted. All psychotropic medications were to be appropriately tapered and discontinued at least 3 days before initiating the study drug.

Efficacy Assessments

Efficacy was assessed using the Montgomery-Åsberg Depression Rating Scale [14] (MADRS; score range: 0–60, with higher scores indicating more severe depressive symptoms), Young Mania Rating Scale [15] (YMRS; score range: 0–44, with higher scores indicating greater severity of manic symptoms), and Hamilton Anxiety Rating Scale [16] (HAMA; score range: 0–56, with higher scores indicating more severe anxiety symptoms) at baseline and at weeks 2, 4, 6, and 8. Additionally, the Sheehan Disability Scale [17] (SDS; score range: 0–30, with higher scores indicating greater functional impairment) and Generalized Anxiety Disorder 7-item scale [18] (GAD-7; score range: 0–21, with higher scores indicating more severe anxiety symptoms) were applied for subjective evaluation of functional impairment and anxiety symptom severity, respectively. The MINI 7.0.2 was utilized to confirm diagnostic eligibility for study enrollment. All assessments were administered by qualified psychiatrists (with at least 5 years of psychiatric clinical experience, or holding the rank of attending physician or higher). Prior to study initiation, all raters completed standardized scale training. Satisfactory interrater reliability was confirmed, with an intraclass correlation coefficient (ICC) greater than 0.8.

Safety and Tolerability Evaluations

Extrapyramidal symptoms were evaluated using the Barnes Akathisia Rating Scale [19] (BARS; range: 0 to 14; with higher scores indicating greater symptoms of akathisia) and the Abnormal Involuntary Movement Scale [20] (AIMS; range, 0 to 28; rating of 2 or higher on the global severity item indicates evidence of tardive dyskinesia). The Columbia-Suicide Severity Rating Scale [21] (C-SSRS, range, 0–42; higher scores indicating greater suicidal risk) was administered throughout the trial for safety monitoring.

Additional safety assessments collected from participants included blood pressure, pulse, BMI, glucose and lipid metabolic parameters, thyroid hormones, sex hormones, and 12-lead electrocardiography

(ECG).

Statistical Analysis

All statistical analyses were performed according to the intention-to-treat principle. The full analysis set (FAS) consisted of all randomized participants who completed baseline assessments and received at least one dose of study medication.

The primary efficacy endpoint was defined as the change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 8. Secondary efficacy endpoints included the change from baseline in the HAMA, SDS, and GAD-7 total scores at Week 8. In addition, categorical efficacy outcomes, specifically response and remission rates at Week 8, were evaluated. Response was defined as a $\geq 50\%$ reduction from baseline in MADRS total score, and remission was defined as a MADRS total score of ≤ 12 . Safety outcomes included changes from baseline in the YMRS, AIMS, and BARS total scores, as well as the incidence and severity of treatment-emergent adverse events.

The primary hypothesis was that lurasidone would be non-inferior to quetiapine with respect to efficacy. The primary outcome measure was the mean reduction in MADRS total score from baseline to Week 8 in both the lurasidone and quetiapine treatment groups. The parameters used for sample size calculation were as follows: one-sided $\alpha = 0.025$, power = 90%, and a 1:1 randomization ratio between the lurasidone and quetiapine groups. The noninferiority margin was set at 2.0; the assumed between-group mean difference was 2.8, with a standard deviation of 5.0 in the lurasidone group and 5.2 in the quetiapine group. Using PASS software, the required sample size was calculated to be $n_1 = n_2 = 25$ per group. To account for anticipated dropouts, a 20% inflation factor was applied, resulting in a required sample size of at least 30 participants per group, for a total sample size of 60 participants to achieve 90% statistical power.

Continuous variables were summarized as mean (standard deviation [SD]) or median (interquartile range [IQR]). Categorical variables were summarized as frequencies and percentages. Baseline characteristics between the lurasidone and quetiapine groups were compared using the χ^2 test, independent-samples t test, or Wilcoxon rank-sum test, as appropriate. Treatment effects on response and remission rates were analyzed using the χ^2 test. Mean reductions from baseline in MADRS, HAMA, SDS, YMRS, GAD-7, AIMS and BARS scores over time were evaluated using a mixed-effects model for repeated measures (MMRM). Treatment group, time, and the group-by-time interaction were included as fixed effects in the model. Time was included as a random effect, with variation permitted for both intercept and slope. All statistical tests were two-sided, and $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). Statistical analyses were conducted between April 2024 and June 2026. This randomized controlled trial was reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Results

Patients and Disposition

A total of 76 participants were screened from August 2021 to March 2024; 16 participants were excluded prior to randomization, including 5 who did not meet the criteria for depressive episode, 3 with MADRS score less than 22 points, 4 with suicidal ideation scores greater than or equal to 4 points, and 4 with inconvenient time for participation. Of the remaining participants, 60 were randomly assigned to treatment with lurasidone (N = 30) or quetiapine (N = 30) (Fig. 1). In the lurasidone group, 1 participant was randomized but not dosed; 4 participants discontinued the study (1 due to lack of efficacy, 1 due to adverse event, 2 due to study drug non-compliance), leaving 25 participants who completed the study. In the quetiapine group, 3 participants were randomized but not dosed; 3 participants discontinued the study (2 lost to follow-up, 1 due to study drug non-compliance), leaving 23 participants who completed the study. The first participant provided informed consent in October 2023, the last participant enrolled in February 2024, and the final study visit was conducted on March 25, 2024.

Baseline demographic and clinical characteristics were similar for the two treatment groups (Table 1). The majority of participants were female (42 of 55 participants [76.36%]), with a mean (SD) age of 19.04 (2.89) years. Of these 55 participants with baseline data, 11 had a diagnosis of bipolar I depression, and 44 had bipolar II depression. The mean (SD) age at the onset of the first episode was 15.44 (2.95) years. The mean (SD) number of mood episodes was 5.24 (3.57), with manic episodes of 1.00 (2.10), hypomanic episodes of 1.47 (1.88), depressive episodes of 3.16 (2.13), and mixed episodes of 0.15 (0.50). The mean baseline MADRS total score for all participants was 30.69.

The mean daily dose of study medication during the study was 35.17 mg in the lurasidone group and 99.62 mg in the quetiapine group. The lurasidone group had a dosage range of 20 mg to 40 mg, while the quetiapine group had a dosage range of 12.5 mg to 300 mg throughout the treatment period.

Table 1

Baseline demographic and clinical characteristics of participants (full-analysis/intent-to-treat population)

FIGURE 1. Patient Disposition in a Randomized Controlled Trial Comparing Lurasidone and Quetiapine for Bipolar Depression

Demographic characteristics	Lurasidone n = 29	Quetiapine n = 26	Mean difference
Age,mean (SD), y	19.10 (2.94)	18.96 (2.83)	0.857
Gender			
Male, n (%)	3 (10.34%)	10 (38.46%)	
Female, n (%)	26 (89.66%)	16 (61.54%)	
Education,mean(SD)(y)	13.14 (2.97)	12.96 (3.16)	0.983
Han ethnicity, n (%)	24 (82.7%)	24 (92.31%)	
Smoking history, n (%)	4 (13.79%)	2 (7.69%)	
Clinical characteristics			
BD type			
BD I,n (%)	7 (24.14%)	4 (15.38%)	
BD II,n (%)	22 (75.86%)	22 (84.62%)	
Age at onset, mean (SD), y	15.07 (2.91)	15.85 (2.99)	0.335
Duration of the current episode, mean (SD)(wk)	10.80 (15.57)	15.88 (30.00)	0.465
No. of mood episodes,mean (SD)	4.75 (3.11)	5.72 (3.96)	0.345
No. of manic episodes,mean (SD)	1.04 (2.19)	0.96 (2.05)	0.893
No. of hypomanic episodes,mean (SD)	1.62 (2.18)	1.32 (1.57)	0.579
No. of depressive episodes,mean (SD)	2.88 (2.07)	3.44 (2.20)	0.358
No. of mixed episodes,mean (SD)	0.21 (0.66)	0.08 (0.28)	0.399
No. of hospitalizations,mean (SD)	0.11 (0.57)	0.21 (0.77)	0.00
Comorbidities and family history			
Comorbid physical illness, n (%)	5 (17.24%)	3 (11.54%)	
Family history of psychiatric disorders, n (%)	9 (31.03%)	3 (11.54%)	
Base scores			
MADRS total	31.48 (6.78)	29.81 (4.39)	0.278
YMARS total	2.38 (3.55)	3.12 (3.89)	0.469

Demographic characteristics	Lurasidone n = 29	Quetiapine n = 26	Mean difference
C-SSRS most	1.90 (1.23)	1.65 (1.20)	0.463
HAMA total	23.52 (8.84)	21.12 (5.74)	0.233
SDS total	6.14 (1.62)	5.69 (2.20)	0.402
AIMS total	0.34 (1.17)	0.35 (1.02)	0.996
BARS total	1.83 (2.47)	2.46 (3.04)	0.403
GAD total	8.69 (7.25)	10.31 (5.58)	0.355
MADRS, Montgomery-Åsberg Depression Rating Scale (10-item); YMRS, Young Mania Rating Scale; C-SSRS, Columbia-Suicide Severity Rating Scale; HAMA, Hamilton Anxiety Rating Scale; SDS, Sheehan Disability Scale; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; GAD-7, Generalized Anxiety Disorder 7-item scale; BD, bipolar disorder.			

Efficacy

Primary Outcomes

Primary efficacy analyses were performed on the modified intention-to-treat (mITT)/full analysis set (FAS) using a mixed-effects model for repeated measures (MMRM). The least squares mean changes from baseline to Week 8 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score were comparable between the lurasidone and quetiapine groups (mean [SE], -19.12 [1.80] vs -14.74 [1.87]; mean difference = - 4.38, 95% CI [- 8.67, 2.24], P = 0.098) (Fig. 2). No significant between-group differences in MADRS score changes were identified at the subsequent study time points, including Weeks 2, 4, and 6 (Table 2).

Additional ITT analyses were conducted to verify the consistency of the primary outcomes. A hybrid linear mixed-effects model produced findings consistent with the primary MMRM analysis. Further sensitivity analysis incorporating group-by-time interaction terms demonstrated no significant interaction effect (F = 3.36, P = 0.0678), confirming the robustness of the primary study results.

Table 2
. The results of the Linear Mixed-Effects Model

FIGURE 2. Least Squares Mean Change in MADRS Total Score From Baseline to Week 8 Between the Two Treatment Groups

Variables	F	P
V1_MADRS	16.63	0.0002
age	0.18	0.6736
sex	5.62	0.0216
Education_level_year	3.11	0.0841
BD_type	0.23	0.6373
time	196.13	< .0001
group	0.00	0.9643
time*group	3.36	0.0678

Secondary Outcomes

No significant between-group differences in response and remission rates were observed at Week 8. Consistent with the primary endpoint, nonsignificant differences in MADRS score changes were maintained at all study visits from Week 2 through Week 8 (Fig. 3).

Anxiety symptoms assessed by the Hamilton Anxiety Rating Scale (HAMA) demonstrated similar improvements across treatment groups. The least squares mean change in HAMA total score from baseline to Week 8 was comparable between the two groups (mean [SE]: -13.64 [1.77] vs -10.32 [1.89]; $P = 0.21$), with no significant differences observed at Weeks 2, 4, and 6.

Subjective anxiety symptoms measured by the Generalized Anxiety Disorder 7-item (GAD-7) scale showed no significant intergroup differences. The least squares mean reduction in GAD-7 scores from baseline to Week 8 was similar for both groups (mean [SE]: -3.96 [1.13] vs -4.35 [1.18]; $P = 0.81$), and no superior effects were identified at any earlier follow-up time point.

Social functioning assessed by the Sheehan Disability Scale (SDS) yielded consistent nonsignificant findings. The least squares mean change in SDS scores from baseline to Week 8 was comparable between the two groups (mean [SE]: -7.52 [1.44] vs -4.61 [1.50]; $P = 0.17$). No significant between-group differences in SDS score improvements were observed across all study visits.

FIGURE 3. Baseline-to-Endpoint Change Scores on Additional Secondary Efficacy Measures (intent-to-treat population)

Safety

No serious treatment-related adverse events occurred throughout the study period. With regard to treatment-emergent adverse events, the lurasidone group demonstrated significantly higher incidences of akathisia, parkinsonism, nausea, and anxiety relative to the quetiapine group. In contrast, somnolence

was more frequently reported in the quetiapine group (Table 3). Vital signs, including blood pressure and heart rate, as well as body weight and body mass index, showed no statistically significant changes from baseline and no notable differences between the two treatment groups. Similarly, laboratory parameters covering complete blood count and biochemical remained comparable across groups throughout the trial.

YMRS scores were similar at all post-baseline study visits between the lurasidone and quetiapine groups (mean [SE]: -0.2 [0.77] vs -0.35 [0.8]; P = 0.90), indicating a low overall risk of treatment-emergent manic switch in both cohorts. Additionally, scores on the AIMS (mean [SE]: -0.08 [0.14] vs -0.17 [0.15]; P = 0.65) and BARS (mean [SE]: 0.44 [0.75] vs -0.65 [0.79]; P = 0.32) were comparable between the two groups at all follow-up time points, with no significant intergroup differences, with only divergent adverse event spectra. The lurasidone group had higher incidences of akathisia, parkinsonism, anxiety and nausea, while somnolence was more common in the quetiapine group. Furthermore, longitudinal assessments using the C-SSRS revealed no significant between-group differences in suicidal risk levels from baseline to Week 8, and both groups sustained low and stable suicidal risk status during the entire treatment course.

Table 3
Adverse Events

Any adverse event	Lurasidone	Quetiapine
	n = 25	n = 23
	18(72%)	17(74%)
Akathisia	7(28%)	0
Somnolence	1(4%)	14(61%)
Dry mouth	1(4%)	1(4%)
Parkinsonism	5(20%)	0
Anxiety	6(24%)	2(9%)
Nausea	7(28%)	0
Constipation	0	1(4%)
Tachycardia	0	2(9%)
Others	2(8%)	1(4%)

Discussion

This single-center, flexible-dose randomized clinical trial evaluated the short-term efficacy and safety profile of lurasidone relative to quetiapine for the treatment of bipolar depression in adolescents and

young adults. The primary endpoint was defined as changes in the Montgomery-Åsberg Depression Rating Scale (MADRS) total scores, which was selected for its high sensitivity in detecting longitudinal changes in depressive symptom severity [22]. A total of 55 participants were included in the full analysis set, with balanced baseline demographic and clinical characteristics across treatment groups. The study population was predominantly female, with a mean age in the late-adolescent to young-adult range. Primary efficacy analyses revealed no significant between-group differences in the least squares mean reduction in MADRS total scores from baseline to Week 8, and these comparable outcomes were consistently maintained across all intermediate study visits. Sensitivity analysis incorporating group-by-time interaction terms further confirmed the stability and robustness of the primary findings.

Secondary endpoint assessments further corroborated the comparable therapeutic efficacy of lurasidone and quetiapine. No significant between-group differences were observed in Week-8 treatment response and remission rates, as well as in the magnitude of anxiety symptom reduction assessed via both clinician-rated and self-reported rating scales. Similarly, no significant group disparities were detected in post-treatment social functional recovery. Collectively, these findings suggest that lurasidone and quetiapine may yield comparable short-term improvements in depressive symptoms, anxiety severity, and social function among adolescent and young adult patients with bipolar depression.

In terms of safety and tolerability, no serious adverse events occurred throughout the study period. The two agents exhibited distinct treatment-emergent adverse event profiles. The lurasidone group demonstrated significantly higher incidences of extrapyramidal symptoms and nausea, whereas somnolence was more prevalent in the quetiapine group. Notably, metabolic safety indicators were well balanced between groups. No statistically significant differences were observed in body weight, body mass index, or glucose-lipid metabolic parameters, including serum lipid and glucose levels. A previous randomized, double-blind, active-controlled trial conducted in Korean patients with schizophrenia reported significantly higher rates of glucose-lipid metabolic disturbances in the quetiapine group compared with the lurasidone group, which further supports the influence of dosage and treatment duration on metabolic safety outcomes [23].

Emerging clinical evidence suggests potential cognitive-protective effects of lurasidone in patients with bipolar disorder.[11] Cognitive function was not measured in this study; however, the low sedative burden of lurasidone may support cognitive function and functional recovery in adolescents and young adults, although this requires further investigation [24].

While clinical research focusing on pediatric and adolescent bipolar depression remains limited, existing trials have shown that lurasidone monotherapy effectively reduces depressive symptoms with minimal metabolic disturbances in young populations [25]. A 2022 comparative study conducted by Diao et al. [11] compared lurasidone with quetiapine in young patients with bipolar depression and reported comparable antidepressant efficacy between the two regimens, which is consistent with the core results of the present study. However, that trial reported greater weight gain in the quetiapine arm, inconsistent

with the neutral metabolic outcomes seen in our participants. These inconsistencies are likely attributable to differing dose regimens and demographic heterogeneity among enrolled subjects.

This study analyzed endocrine indicators. No significant between-group differences were found in changes in prolactin and thyroid hormone levels. Previous studies have indicated that atypical antipsychotics may affect endocrine function [26]. This may be explained by multiple factors, including the unique characteristics of young participants, relatively low therapeutic doses, and the short observational duration of the trial [26, 27].

Previous studies have shown that lurasidone is associated with fewer adverse effects and has a smaller impact on weight and metabolism compared with other atypical antipsychotics [28]. In this trial, the most frequently reported treatment-emergent adverse events in the lurasidone group were akathisia and nausea. The overall incidence of treatment-emergent adverse events associated with lurasidone in the present study was slightly elevated relative to data from earlier investigations. Such inconsistency may arise from inter-study heterogeneity in adverse event adjudication criteria, demographic disparities among enrolled populations, and differing dose-titration protocols [29]. Prior comparative studies in adult populations have consistently shown that quetiapine carries a higher risk of metabolic complication [28]. However, no significant metabolic disparities were identified in this study, further indicating that low quetiapine exposure and limited follow-up duration may mitigate short-term metabolic adverse reactions.

Findling et al.[30] conducted a pediatric pharmacokinetic and tolerability trial in children and adolescents with psychiatric disorders. Their results verified that lurasidone is better tolerated at lower doses, particularly in younger children. Our study achieved effective responses with relatively low lurasidone doses, supporting cautious dosing for Chinese children and adolescents.

This study has several key strengths and innovations. Firstly, it targets adolescents and young adults, a cohort mainly composed of students and new professionals. Unlike adults, this population prioritizes avoiding drug-induced sedation, increased appetite, weight gain and endocrine disorders, as these side effects greatly interfere with their study, social functioning and long-term physical health [31]. In addition, growing evidence validates lurasidone's cognitive-improving effects, which carry important clinical significance for youths in critical developmental periods [24].

Secondly, this study adopted a rigorous head-to-head, active-controlled design, which is particularly meaningful given that direct high-quality comparative data between lurasidone and quetiapine in adolescent bipolar depression remain scarce. As a first-line drug with proven efficacy for bipolar depression [32], quetiapine acts as an ideal control to objectively assess the efficacy and safety of lurasidone. This design greatly strengthens the reliability and clinical translational value of our results.

In summary, this study offers meaningful evidence to optimize individualized treatment and rational dosing for bipolar depression in adolescents and young adults.

Several limitations should be noted for cautious result interpretation. First, mild baseline gender imbalance between groups may cause confounding bias. Second, the maximum lurasidone dose was restricted to 40 mg, precluding observation of dose-dependent adverse events at higher doses. Third, the short-term design cannot fully evaluate long-term sustained efficacy and delayed adverse reactions [33]. Fourth, the single-center setting weakens the external generalizability of the findings.

Conclusion

In conclusion, lurasidone demonstrates satisfactory efficacy for depressive episodes in adolescents and young adults with bipolar disorder, accompanied by a relatively low risk of specific treatment-emergent adverse events. As a promising therapeutic option for bipolar depression, but more high-quality randomized controlled trials are required to validate the present results and clarify its position in long-term therapeutic regimens [33].

Future research should conduct large-scale, multicenter real-world studies to assess the real-world efficacy and safety of lurasidone in routine clinical practice, which can compensate for insufficient population representativeness in traditional randomized controlled trials [34]. Further exploration is required to confirm its clinical value in younger children, peripartum women and elderly patients with bipolar depression [35]. Moreover, head-to-head randomized controlled trials are urgently needed to compare the efficacy and tolerability between lurasidone and other first-line medications for adolescent bipolar depression. Combined analyses of neuroimaging, pharmacogenomics and inflammatory biomarkers may screen out predictive markers of therapeutic response, so as to promote the development of precision individualized treatment.

Declarations

Ethics approval and consent to participate

The experimental protocol was established according to the ethical guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Beijing Anding Hospital affiliated with Capital Medical University (Approval No.: 2021(55h)-202199FS-2). The study was registered in the Chinese Clinical Trial Registry (ChiCTR2100049426; registered on 02 August 2021). Written informed consent was obtained from all participants or their legal guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Funding

This project was initiated by Beijing Anding Hospital and supported by the Beijing Municipal Administration of Hospitals Cultivation Program. The study was registered in the Chinese Clinical Trial Registry (ChiCTR2100049426). The funder had no role in the study design, data management, analysis, interpretation, or publication of findings. The research proposal, including the design and protocol, has undergone peer review during the funding process. The views expressed in this publication are those of the authors only.

Author Contribution

Wei Wang designed the study. Cong-cong Sun, Dan Wang, and Chun-Feng Xiao drafted the manuscript; Jia Zhou and Mei-Ti Wang analyzed and interpreted the data. Jin-jie Xu conducted the statistical analysis, revised the manuscript, a literature review and supervised the study. Li-juan Yang, Yu Qiao, Jin-he Zhang, Yan-li Pan, Shuang Liu, Sheng Li, Gao-ming Xie and Chen Hu participated in patient recruitment, clinical data collection, and scale evaluation. All authors reviewed and approved the final version of the manuscript.

Acknowledgement

This study was initiated by Beijing Anding Hospital and supported by the Beijing Hospitals Authority Cultivation Program. We sincerely thank all investigators and clinical staff from the three collaborating centers for their pivotal contributions to the organization and implementation of this trial. We also gratefully acknowledge all participants for their enrollment and engagement in the study.

Data Availability

The data generated and analyzed in this study are retained by the corresponding author. Restrictions apply to the availability of these data, which are not publicly available due to relevant research confidentiality requirements. However, the datasets supporting the findings of this study are available from the corresponding author upon reasonable request and with formal permission for academic research purposes.

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Figures

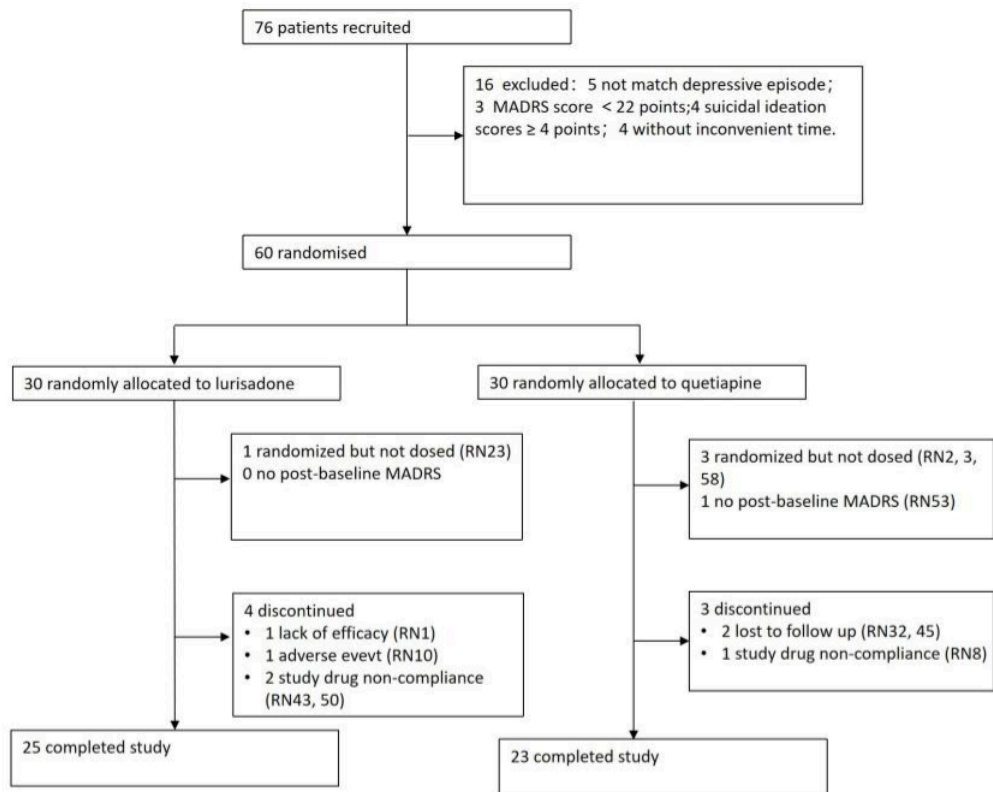


Figure 1

Patient Disposition in a Randomized Controlled Trial Comparing Lurasidone and Quetiapine for Bipolar Depression

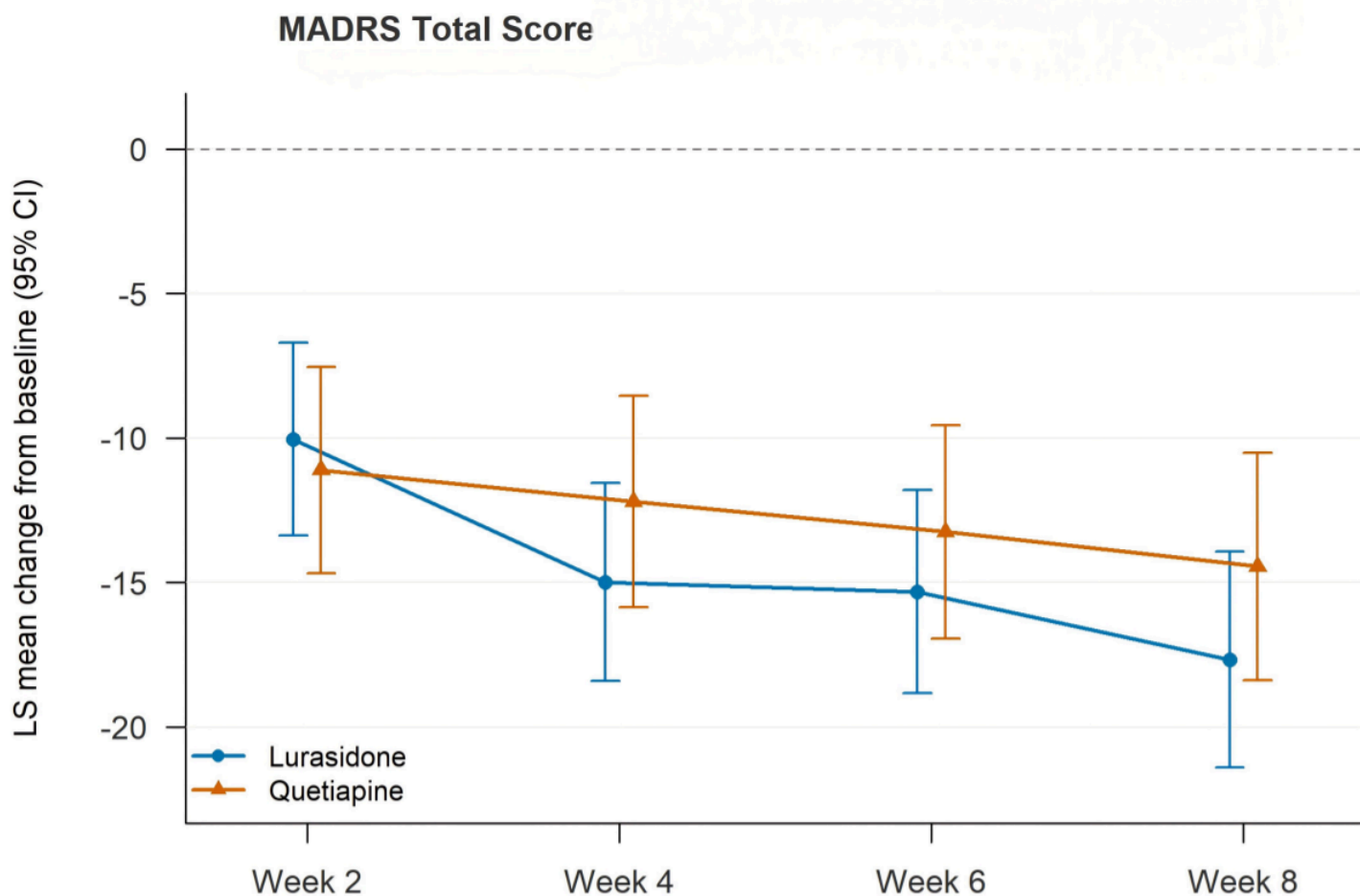


Figure 2

Least Squares Mean Change in MADRS Total Score From Baseline to Week 8 Between the Two Treatment Groups

Secondary Outcomes: Model-Adjusted Change Through Week 8

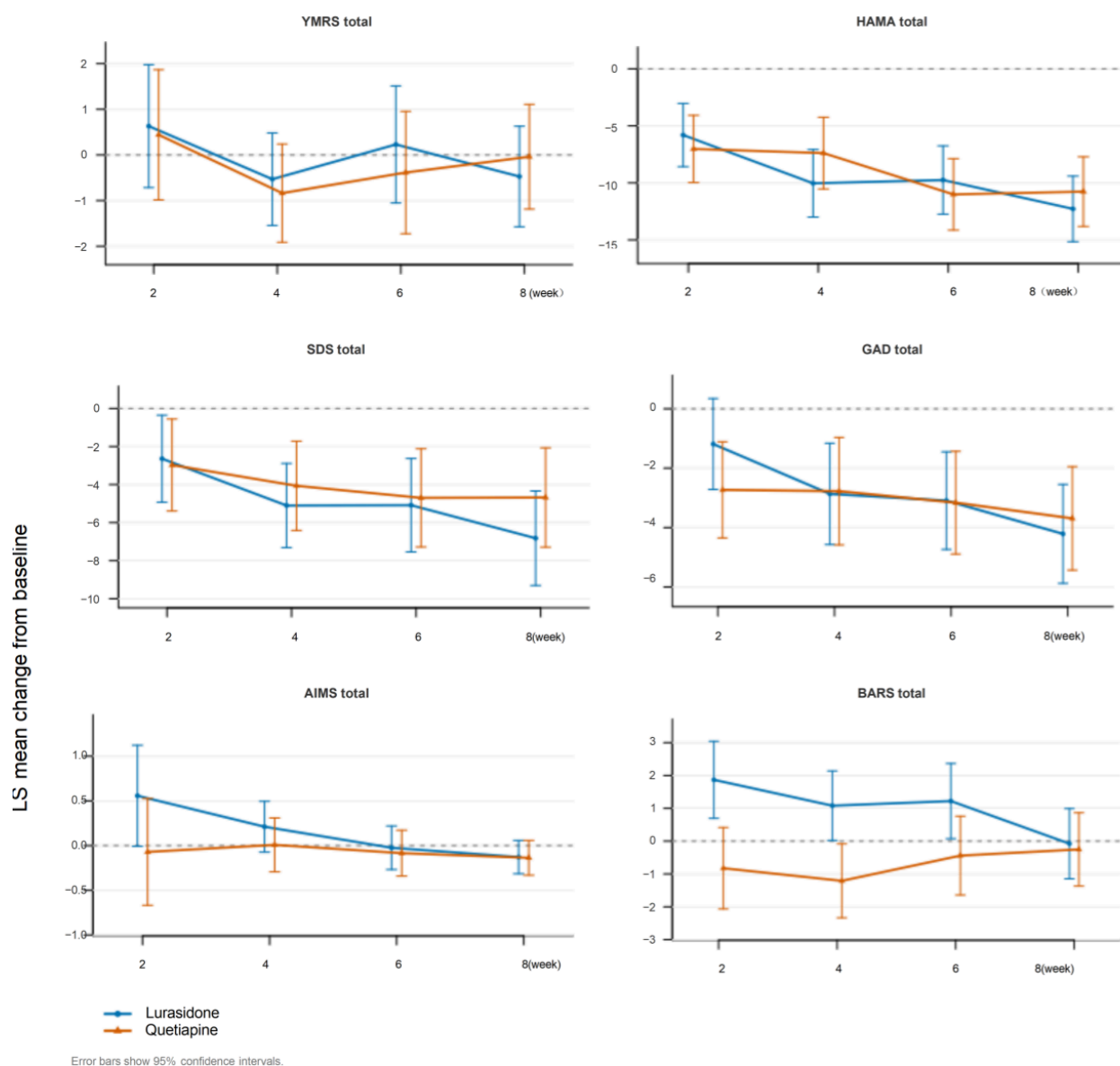


Figure 3

Baseline-to-Endpoint Change Scores on Additional Secondary Efficacy Measures (intent-to-treat population)

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