Effect of antipsychotics and mood stabilisers on metabolism in bipolar disorder: a network meta-analysis of randomised-controlled trials

Lingzhuo Kong,[a,j] Huaizhi Wang,[b,j] Ning Yan,[a,c] Chenyue Xu,[a] Yiqing Chen,[a] Yuanyuan Zeng,[d] Xiaonan Guo,[a] Jing Lu,[a,e,f,g,h,**] and Shaohua Hu[a,b,e,f,g,h,i,*]

[a]Department of Psychiatry, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, 310003, China
[b]School of Psychiatry, Wenzhou Medical University, Wenzhou, 325000, China
[c]Shanghai Jing 'an District Mental Health Centre, Shanghai, 200040, China
[d]Hangzhou Medical College, School of Clinical Medicine, Hangzhou, 310003, China
[e]Zhejiang Key Laboratory of Precision Psychiatry, Hangzhou, 310003, China
[f]Brain Research Institute of Zhejiang University, Hangzhou, 310003, China
[g]Zhejiang Engineering Centre for Mathematical Mental Health, Hangzhou, 310003, China
[h]MOE Frontier Science Centre for Brain Science & Brain-Machine Integration, Zhejiang University, Hangzhou, 310003, China
[i]Department of Psychology and Behavioral Sciences, Zhejiang University, Hangzhou, 310003, China

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Summary

Background Antipsychotics and mood stabilisers are gathering attention for the disturbance of metabolism. This network meta-analysis aims to evaluate and rank the metabolic effects of the commonly used antipsychotics and mood stabilisers in treating bipolar disorder (BD).

Methods Registries including PubMed, Embase, Cochrane Library, Web of Science, Ovid, and Google Scholar were searched before February 15th, 2024, for randomised controlled trials (RCTs) applying antipsychotics or mood stabilisers for BD treatment. The observed outcomes were twelve metabolic indicators. The data were extracted by two reviewers independently, and confirmed by another four reviewers and a corresponding author. The above six reviewers all participated in data analyses. Data extraction was based on PRISMA guidelines, and quality assessment was conducted according to *the Cochrane Handbook*. Use a random effects model for data pooling. The PROSPERO registration number is CRD42023466669.

Findings Together, 5421 records were identified, and 41 publications with 11,678 complete-trial participants were confirmed eligible. After eliminating possible sensitivity, risperidone ranked 1st in elevating fasting serum glucose (SUCRA = 90.7%) and serum insulin (SUCRA = 96.6%). Lurasidone was most likely to elevate HbA1c (SUCRA = 82.1%). Olanzapine ranked 1st in elevating serum TC (SUCRA = 93.3%), TG (SUCRA = 89.6%), and LDL (SUCRA = 94.7%). Lamotrigine ranked 1st in reducing HDL (SUCRA = 82.6%). Amisulpride ranked 1st in elevating body weight (SUCRA = 100.0%). For subgroup analyses, quetiapine is more likely to affect indicators of glucose metabolism among male adult patients with bipolar mania, while long-term lurasidone tended to affect glucose metabolism among female patients with bipolar depression. Among patients under 18, divalproex tended to affect glucose metabolism, with lithium affecting lipid metabolism. In addition, most observed antipsychotics performed higher response and remission rates than placebo, and displayed a similar dropout rate with placebo, while no between-group significance of rate was observed among mood stabilisers.

Interpretation Our findings suggest that overall, antipsychotics are effective in treating BD, while they are also more likely to disturb metabolism than mood stabilisers. Attention should be paid to individual applicability in clinical practice. The results put forward evidence-based information and clinical inspiration for drug compatibility and further research of the BD mechanism.

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*Corresponding author. Department of Psychiatry, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, 310003, China.
**Corresponding author. Department of Psychiatry, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, 310003, China.
E-mail addresses: dorhushaohua@zju.edu.cn (S. Hu), lujing2016@zju.edu.cn (J. Lu).
[j]These authors contributed equally.

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Research in context

Evidence before this study

We searched 6 registries (PubMed, Embase, Cochrane Library, Web of Science, Ovid, and Google Scholar) up to February 15th, 2024 based on the keywords ("bipolar disorder" OR "bipolar disorders" OR "bipolar mood disorder" OR "manic depressive psychosis" OR "manic depression") AND ("antipsychotic agents" OR "major tranquillizing agents" OR "antipsychotics" OR "mood stabiliser" OR "mood stabilising drug"), without restrictions of language, age, race, nationality, completion rate of the trials, or the current mood states. Eligibility criteria include applicable full text and data, randomised-controlled design, participants with a first psychiatric diagnosis of bipolar disorder, intervention of antipsychotics or mood stabiliser, and reported metabolic indicators. Together, 41 publications with 11,678 complete-trial participants were confirmed eligible for analysis, among which 4 trials were assessed high risk of performance or attrition bias. There are 17 interventions (lithium, valproic acid, divalproex, lamotrigine, topiramate, zonisamide, quetiapine, lurasidone, aripiprazole, ziprasidone, risperidone, olanzapine, haloperidol, asenapine, cariprazine, lumateperone, and amisulpride) included in the network meta-analysis, including 11 antipsychotics and 6 mood stabilisers.

Added value of this study

This is the first study, to our knowledge, to incorporate a comprehensive ranking of antipsychotics and mood stabilisers by their influence on the metabolism, and to describe the difference in metabolic effects of these drugs among subgroups with different characteristics at the baseline. The results estimate that antipsychotics are more likely to disturb metabolism but also display better therapeutic effects, compared to mood stabilisers. Meanwhile, quetiapine tends to affect glucose metabolism among male patients with bipolar mania, while lurasidone tends to affect glucose metabolism among female patients with bipolar depression. Among adolescent patients, divalproex tends to affect glucose metabolism, and lithium affects lipid metabolism.

Implications of all the available evidence

When applying pharmacotherapies to patients with bipolar disorder, attention should be paid to the metabolic disturbance of antipsychotics and individual applicability, especially the difference in metabolic reaction between different sexes, ages, and current episodes.

Introduction

Bipolar disorder (BD), a severe, disabling, and high-mortality psychiatric disorder characterised by fluctuating mood states and behavior, affects more than 2% of the global population,[1] especially adolescents,[2] burdening the medical and social welfare institutions for tens of billions of dollars annually.[3] Given the complex interaction between neurons, glia, sub-cellular components, and inflammatory molecules in the central and peripheral micro-environment,[4–7] challenge remains in uncovering the underlying mechanism of BD, as well as establishing therapeutics of higher credibility and precision.[8] Although emerging adjuvant or alternative pharmacotherapies are gathering interest,[9] antipsychotics (mostly second-generation) and mood stabilisers remain the most common pharmacotherapies for BD in clinical practice.

Antipsychotics mainly target neurotransmitter systems, particularly the dopamine, 5-HT, GABA, and noradrenaline circuits that are associated with affective regulation in the frontal-limbic regions (including the hippocampus, amygdala, septum, orbitofrontal gyrus, hypothalamus, dentate gyrus, and cingulate gyrus, etc.),[10] in which they modulate the intracellular signaling cascade, protein translation, and epigenetic modification of genes.[11] The pharmacological mechanism of mood stabilisers has yet to be completely elucidated.

Although the efficacy of antipsychotics and mood stabilisers for BD has been confirmed,[12,13] the metabolic effects of these drugs raise another dilemma. Increased risks of obesity, dyslipidaemia, diabetes, and weight gain have been frequently reported among patients of all age groups treated with these drugs.[14,15] Previous studies revealed that antipsychotics interfered with the neural centre for energy balance regulation by acting on dopamine and serotonin (5-HT) receptors, which in turn increased appetite for food rich in sweets and fat.[16] Antipsychotics also affect neurotransmission mediated by 5-HT, which has been confirmed to be associated with metabolic disturbance and weight gain.[15] It is also reported that the intra- and inter-cellular signaling mediated by antipsychotics attenuates insulin sensitivity of muscular cells and adipocytes, as well as influences endogenous glucose production, glucose uptake, and insulin secretion, which eventually increases the risk of obesity and diabetes.[15–18] Antipsychotics might also promote the proliferation and differentiation of adipose tissue, contributing to abnormalities in glucose and

lipid metabolism.[15,18,19] As for mood stabilisers, evidence suggests that long-term lithium intervention might lead to glucose tolerance impairment and insulin resistance, which might be attributed to the inhibition of glucophosphomutase.[20–23] It was also reported that lithium could induce lipoprotein metabolism dysfunction and elevate serum levels of low-density lipoprotein cholesterol (LDL).[24] Furthermore, combined therapy of antipsychotics and mood stabilisers showed more metabolic effects than monotherapy of mood stabilisers.[25]

Lithium, valproic acid, carbamazepine, lamotrigine, and topiramate have previously been ranked based on the risk of developing secondary metabolic disorders.[26] In clinical practice, mood stabilisers are often co-intervened with antipsychotics among patients with BD. However, to date, no comprehensive ranking of the metabolic effects of these two types of drugs has been carried out. Moreover, new drugs with concerns over their metabolic effects (such as lumateperone) have been recently approved for BD treatment, suggesting the previous rankings to be updated.

Network meta-analysis (NMA) presents an evidence-based method for the direct and indirect comparisons of multiple interventions on the same parameter, thus putting forward evidence-based information for clinical application.[27] This NMA aims to 1) evaluate and rank the metabolic effects of commonly used antipsychotics and mood stabilisers among patients with BD with different baseline characteristics; 2) provide therapeutic recommendations for clinical practice.

Methods

Protocol, registration, and ethics

The protocol of this study was registered with the PROSPERO database of systematic reviews (CRD42023466669)[28] after the preliminary searches started. The NMA and the systematic literature review were carried out following the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses.[29] Ethics approval was not required since the study was an analysis of published RCTs.

Search strategy

The search for published randomised-controlled trials (RCTs) on the pharmacotherapies of BD using antipsychotics and mood stabilisers was conducted in PubMed, Cochrane Library, Embase, Web of Science, Ovid, and Google Scholar. Systematic retrieval using MeSH terms was carried out in the former four databases, with manual retrieval in the latter two databases.

All databases were searched from their inception to February 15th, 2024. The strategy used terms covering all of the commonly used antipsychotics and mood stabilisers. Before conducting the analysis, the balance between sensitivity (the ability to identify all studies on a specific topic) and specificity (the ability to exclude irrelevant studies from the primary search results) was carefully considered. The decision was made to utilise a broad, population-based approach to the search to maximise the retrieval. In consideration of the large quantity of search results, we used limiting filters based on the type keyword "clinical trial", "controlled clinical trial", or "randomised-controlled trial" when appropriate, and the search field was limited to "Title/Abstract" in PubMed. In the detailed screening, only randomised-controlled trials were preserved.

Supplementary Appendix 1 provided complete information on search terms, the search strategy of PubMed, and details of the PICOS outline.

Eligibility criteria

Inclusion criteria:

1) Full text and data could be obtained;
2) Designed in RCT;
3) The first psychiatric diagnosis of the patient was bipolar disorder;
4) Pharmacological interventions included mood stabilisers or antipsychotics;
5) Outcomes included metabolic indicators.

Exclusion criteria:

1) Data of metabolic indicators were not presented as continuous variables;
2) Patients reported primary metabolic disorder (e.g., diabetes), liver dysfunction, endocrine diseases, and neuropathologic diseases, as well as women in pregnancy or lactation;
3) Baseline medication could significantly influence metabolism (e.g., contraceptive drugs, hormone supplements);
4) Any other items contrary to the inclusion criteria.

Baseline medication for affective disorders is limited to antidepressants, and RCTs involving augmentation, adjunct therapies, or physical therapies were excluded. To best inform clinical practice, we purposefully included all RCTs comparing any antipsychotics or mood stabilisers versus placebo, as well as head-to-head comparisons within or between the two types of drugs. There is no limitation on language, age, race, nationality, completion rate of the trials, or the current mood states (euthymia, mania, hypomania, mixed state, or depression). The diagnosis of BD should be based on standard diagnostic criteria including the *Diagnostic and Statistical Manual of Mental Disorders III* (*DSM-III*), *DSM-IV*/*DSM-IV-TR*, *DSM-V*, and *ICD-10* (with or without other assessing tools, such as baseline psychiatric scales). Head-to-head trials that met the inclusion criteria were also considered eligible.

Assessed outcomes

Main outcomes are changes in the indicators of glucose and lipid metabolism, including fasting serum glucose, serum insulin, Hemoglobin A1c (HbA1c), total cholesterol (TC), total triglyceride (TG), high density lipoprotein cholesterol (HDL), and LDL. The pharmacological interventions were ranked along with their ability to increase the levels of these indicators, except for HDL. As for HDL, ranking of the interventions was conducted by the ability to reduce serum HDL levels since lower levels of HDL were associated with health risk.

Additional outcomes include anthropometric measurements (body weight, BMI, and waist circumference), total serum bilirubin, and serum prolactin, which are also regarded as metabolism-related indicators.

In order to put forward more comprehensive ranking results, mean surface under the cumulative ranking curve (SUCRA) and mean ranking of fasting serum glucose, TC, TG, LDL, and body weight were further analysed based on the results after eliminating sensitive comparisons. Only interventions with applicable data of all these indicators were ranked and presented.

Efficacy estimation included rate of response (demonstrated as the reduction of scale scores to a specific percentage) and full remission (demonstrated as the scale scores reached a particular number). Tolerability was defined as the proportion who dropped out due to any cause during the entire trial.[30] Head-to-head studies were excluded from rate analyses due to the absence of the controlled (placebo) group. Results of rate analyses were supplied in Supplementary Results.

Subgroup analyses were conducted on the representative indicators, including fasting serum glucose, serum insulin, HbA1c, TC, and body weight. The subgroups include age (≤18 years old, or > 18 years old), sex ratio (percentage of male ≤50%, or >50%), race (percentage of white/Caucasian/Native American ≤50%, or >50%), current episode (mania/hypomania/mixed state, or depression), intervention duration (≤6 weeks, or >6 weeks), and baseline medication (with baseline medication when recruited in the trial, or medication washed-out). Baseline medication refers to medication for physical or non-physical diseases except for benzodiazepines, antidepressants, or drugs for reducing the adverse effect of the observed interventions. Age-based subgroup analyses on TG and serum prolactin were additionally conducted in consideration of their importance, particularly for the youths, while only fasting serum glucose, TC, and body weight were analysed for race subgroups since few trials recruited more non-white participants than white participants.

Data collection and quality assessment

Data extraction was started on October 4th, 2023, and was done by two reviewers (LZK and HZW) independently. Four reviewers (NY, CYX, YQC, and YYZ) and a corresponding author (SHH) confirmed the summarised data. The extraction of information including authors, publication year, baseline characteristics of the participants (age, sex ratio, and current episode), race distribution, diagnostic guidelines, study duration, sample size, interventions, study results, and baseline medication. Baseline information was collected and summarised based on intention-to-treat (ITT) analysis (defined as participants who violate the study protocol or drop out are considered as belonging to the treatment arm that they were originally randomised to).[31] Graphed data were extracted by Engauge Digitizer. If the necessary data could not be obtained from the publications, we contacted the authors for further information. Six reviewers (LZK, HZW, NY, CYX, YQC, and YYZ) participated in the data analyses.

To ascertain the validity of eligible RCTs, at least two reviewers independently assessed the risk of bias according to *the Cochrane Handbook Risk of Bias Tool for RCTs*, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias.[32] By intensively reviewing the primary publications, we conducted two visual quality assessment figures via Review Manager version 5.4.1.

Consistency checks and publication bias assessment

In the NMA, a fundamental assumption is that the same parameter was estimated by direct and indirect evidence. For example, if the analysis aims to compare intervention A and B, then the direct comparison of A versus B is the same as indirect comparisons of A versus C and B versus C ideally. When a conflict between the direct comparison and indirect evidence (comprehensively analysing the result of A versus C and B versus C), inconsistency (also known as similarity or transitivity assumption) arises.[33]

Inconsistency was checked via comparisons between the standard network consistency model[34] or an unrelated mean effects model,[35] which is also known as the inconsistency model. This model significantly reduces heterogeneity and improves model fit, since it allows separate and unrelated meta-analyses for every pair-wise contrast with a shared variance parameter in the random effects model.[34] In this NMA, the node splitting method is used to evaluate the consistency between the direct and indirect evidence. The comparison was defined as inconsistent when $p < 0.05$.

Publication bias (described as the phenomenon that trials with small sample sizes and negative results are more difficult to publish than large-cohort trials with positive results) across studies was assessed via the funnel plot of the trial effect sizes for asymmetry. The funnel plot was conducted in all network comparisons, and symmetry was used to evaluate publication bias.

Network meta-analysis

A network of publications applying antipsychotics and mood stabilisers on patients with BD, for which data on the changes in metabolic indicators listed above, were designed. The flow diagram for the NMA is provided in Fig. 1.

The variables of all the primary data extracted from the publications were continuous, and were presented as mean change (from baseline to endpoint of the RCT period) with SD. In this NMA, continuous variables were reported as standardised mean difference (SMD) (the quotient of the difference between two independent means and the combined standard deviation), which is applied for the combination of RCTs with different evaluating methods, along with the 95% credible interval (CI). The normal likelihood was used for continuous outcomes. Data of response rate, remission rate, and rate of adverse events was unified as number of occurred events and number of no events occurrence. Relative risk (RR) and 95% CI were used for pooling binary variables. Given the inevitability of potential crossing-study differences, the random-effect model was applied. Results were not highlighted if one end of the 95% CI reached the invalid line. Moreover, if more than one eligible experimental groups were contained in one study, number of the participants in the controlled groups was divided. The post-division sample size was in accord with the sample size of each experimental group, with SMD, SD, or rate unchanged.

For rate analyses, heterogeneity among the included studies was assessed using the I^2 index, with an I^2 of 25%, 50%, and 75% indicating mild, moderate, and high heterogeneity, respectively, and was shown in the forest plots. $I^2 > 50\%$ was considered high heterogeneity. In the network analysis, we assumed that heterogeneity was the same for all intervention comparisons. The range of 95% CI in the league tables visually reflects the heterogeneity of the network comparisons.

According to the PRISMA manual of NMA, Markov Chain Monte Carlo simulation chains in the Bayesian-based framework were used to perform the meta-aggregation.[36,37] STATA (SE) version 15.1 was applied for data analysis and figure formation. In the network map, each node represents a pharmacological intervention, and their connections refer to the head-to-head comparisons. The area of the nodes is in accord with the

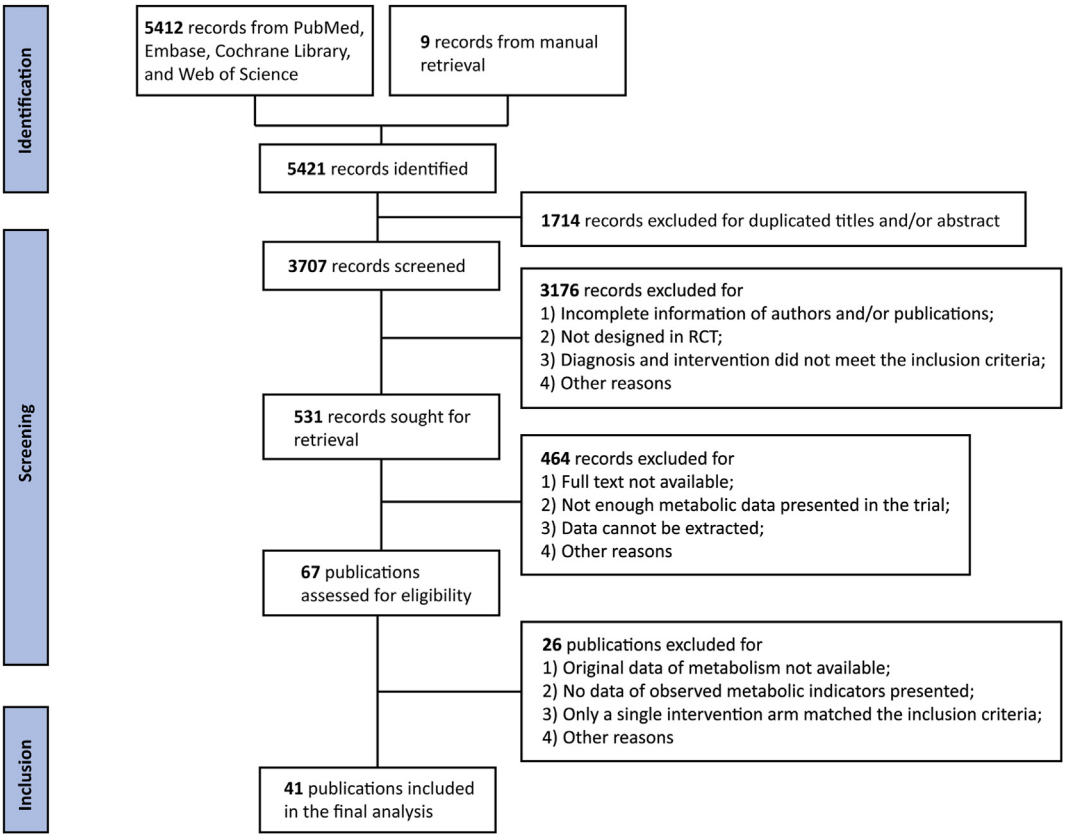

Fig. 1: **Flow diagram of the network meta-analysis**. Published studies before February 15th, 2024 were searched using standardised strategy. In total, 5421 records were identified from the databases. After duplication movement and detailed screening according to the inclusion and exclusion criteria, 41 publications were eventually included in the network meta-analysis. Abbreviation: RCT: randomised-controlled trial.

number of participants, and the width of their connections is in accordance with the number of direct comparisons. Data analyses were based on the last observation carried forward (LOCF),[38,39] an acknowledged method for end point analysis, which is defined as the participants who drop out of the study halfway, their last valid scores were carried forward until the end of the study.[40]

The hierarchy of the pharmacological interventions was presented as P score. The P score refers to SUCRA, which is given in percentage and represents the superiority of the corresponding intervention. The interventions were ranked by the ability to evaluate the serum levels of each metabolic indicator. P score ranges from 0 to 1. Of note, although the P score provides a feasible method for estimating the metabolic effects of the interventions, careful and comprehensive consideration of variable clinical scenarios is in demand for weighting the practical benefit and the potential metabolic effects.

Sensitivity checks

Sensitivity checks are carried out by eliminating comparisons of possibly high risk of sensitivity. The eliminated comparisons are those located on the edge of the funnel plots. RCTs evaluated to "high risk of bias" through quality assessment were also eliminated for sensitivity. Sensitivity checks were applied in all analyses when feasible (sufficient data were applicable) and necessary (funnel plots showed visually significant bias).

Role of the funding source

The funders of this study had no role in the study design; collection, analysis, and interpretation of data; writing of the report; and decision to submit the article for publication. All authors confirmed that they had full access to all the data in the study and accepted responsibility for the decision to submit for publication.

Results

Identified publications

In total, 41 eligible studies evolving 11,678 complete-trial participants were enrolled in the NMA. The interventions include lithium, valproic acid, divalproex, lamotrigine, topiramate, zonisamide, quetiapine, lurasidone, aripiprazole, ziprasidone, risperidone, olanzapine, haloperidol, asenapine, cariprazine, lumateperone, and amisulpride (Fig. 1).

Among all the studies, 14 reported baseline medication of antipsychotics or mood stabilisers. One used extended-release agents of quetiapine (Findling RL et al., 2014, N = 144), one used combined olanzapine and fluoxetine (Brown E et al., 2009, N = 410), and another one was three-arm designed (olanzapine monotherapy, olanzapine in combination with fluoxetine, and placebo, Tohen M et al., 2003, N = 706), in which only data of olanzapine monotherapy and placebo were extracted and analysed. These RCTs were retained in the NMA for their contribution to the heterogeneity estimation. Head-to-head trials and post-hoc analyses (defined as analyses of data that has already been collected to perform analyses for new purposes that were not planned initially) were also included.

Characteristics of the enrolled studies, baseline or changed data of the main and additional outcomes, and references were summarised in Supplementary Appendix 2.

Quality assessment, consistency, and publication bias checks

Most of the publications presented a high or unclear risk of bias, while four publications announced bias of detection and attrition. All the direct and indirect comparisons were checked for consistency and inconsistency. Statistically significant inconsistency between some direct and indirect comparisons was detected. According to the funnel plots, significant publication bias was visually observed in some groups.

Detailed information was summarised in Supplementary Appendix 3, 4, and 5.

Main outcomes

Fasting serum glucose, insulin, and HbA1c

Risperidone ranked higher than the remaining interventions, while zonisamide was more likely to elevate fasting serum glucose levels than olanzapine [SMD = 1.28 mmol/L, 95% CI = (0.76, 1.80) mmol/L], and cariprazine was more likely to elevate fasting serum glucose levels than placebo [SMD = 0.09 mmol/L, 95% CI = (0.01, 0.18) mmol/L]. Lumateperone and divalproex both ranked below placebo (Fig. 2a and b).

Among interventions with applicable data of insulin, risperidone ranked 1st, and valproic acid ranked 2nd. After eliminating a sensitive comparison of quetiapine versus placebo, the ranking of quetiapine changed from 5th to 7th. Among interventions with accessible data of HbA1c, significance was observed in lurasidone versus topiramate [SMD = 0.91 pmol/L, 95% CI = (0.06, 1.76) pmol/L], as well as quetiapine versus topiramate [SMD = 0.87 pmol/L, 95% CI = (0.01, 1.72) pmol/L]. After sensitivity checks, quetiapine ranked below placebo.

TC, TG, HDL, and LDL

Most antipsychotics ranked higher than placebo, and all mood stabilisers ranked below placebo in elevating TC levels. After eliminating sensitive comparisons, olanzapine ranked 1st, and significance was noticed between topiramate and zonisamide [SMD = 0.71 mmol/L, 95% CI = (0.06, 1.37) mmol/L]. Olanzapine also ranked 1st in elevating TG levels, and quetiapine ranked significantly higher than zonisamide [SMD = 1.81 mmol/L, 95% CI = (1.06, 2.55) mmol/L]. After eliminating sensitive

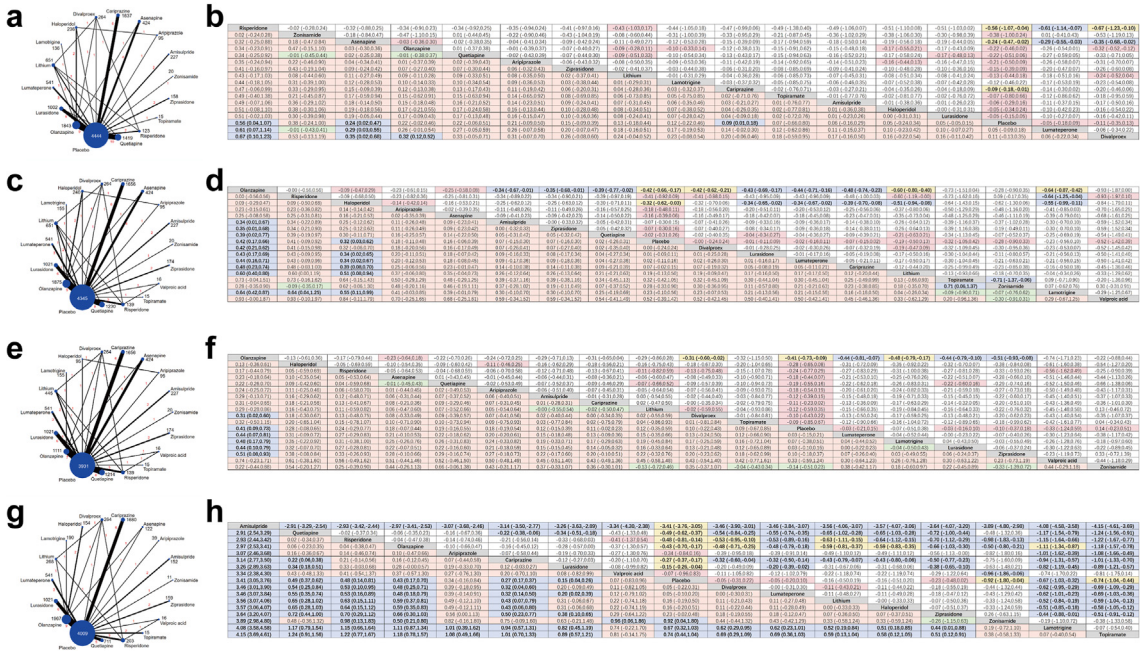

Fig. 2: **Network maps (before sensitivity checks) and league tables (after sensitivity checks) presenting head-to-head comparisons of fasting serum glucose, TC, TG, and body weight**. Mean difference and 95% CI of every individual intervention compared with every other are presented in this figure. The network maps present all interventions with direct comparisons. The size of the blue dots is in accord with the number of participants, and the width of the black line refers to the number of direct comparisons. The league tables present all head-to-head results of the network meta-analysis, in which some comparisons were highlighted. In the lower triangles, comparisons with statistical significance were marked blue. Comparisons of no significance with a positive mean were marked orange, and those with a negative mean were marked green. In the upper triangles, comparisons of statistical significance were marked blue, among which those that had been directly compared were marked yellow. Direct comparisons without statistical significance were marked red. 2a: Network map of fasting serum glucose; 2b: League table of fasting serum glucose; 2c: Network map of TC; 2d: League table of TC; 2e: Network map of TG; 2f: League table of TG; 2g: Network map of body weight; 2h: League table of body weight. Abbreviations: CI: credible interval; TC: total cholesterol; TG: total triglyceride.

comparisons, the number of comparisons with statistical significance was reduced (Fig. 2c–f).

Among interventions with applicable data, only quetiapine, cariprazine, and valproic acid were more likely to reduce HDL levels than placebo. After sensitivity checks, lamotrigine ranked 1st, followed by olanzapine and quetiapine. Haloperidol, asenapine, and olanzapine ranked significantly higher than placebo in elevating LDL levels. After sensitivity checks, olanzapine ranked 1st, and more comparisons with significance were observed.

Additional outcomes

Anthropometric measurements

Antipsychotics ranked higher than mood stabilisers in elevating anthropometric measurements (including body weight, BMI, and waist circumference) (Fig. 2g and h). Amisulpride ranked 1st in elevating body weight, while olanzapine ranked 1st in elevating BMI after eliminating sensitive comparisons. Olanzapine also ranked 1st in elevating waist circumference among all interventions with applicable data.

Serum prolactin and total serum bilirubin

Risperidone ranked 1st in elevating serum prolactin, and significance was noticed in comparisons of most of the interventions versus lumateperone. Cariprazine ranked 1st in elevating total serum bilirubin, but no significance was detected among all comparisons.

Other detailed information of main and additional outcomes was summarised in Supplementary Appendix 4. The summary of mean SUCRA and mean ranking of fasting serum glucose, TC, TG, and body weight is shown in Table 1. Divalproex, asenapine, and valproic acid were absent for lack of data or sensitivity elimination. Most antipsychotics ranked higher than mood stabilisers, and all observed mood stabilisers ranked below placebo. Of note, lumateperone was the only antipsychotics ranking lower than placebo.

Subgroup analyses

Age

Divalproex ranked 1st in elevating fasting serum glucose among the youths, while it ranked last in the adult subgroup [SMD = –0.11 mmol/L, 95% CI = (–0.35, 0.13)

Treatment	SUCRA (%)	Ranking
Olanzapine	85.64 (81.46, 89.82)	3.34 (2.67, 4.01)
Risperidone	72.50 (63.17, 81.83)	5.38 (3.99, 6.77)
Aripiprazole	66.18 (63.51, 68.85)	6.48 (6.11, 6.85)
Quetiapine	65.84 (60.77, 70.91)	6.56 (5.71, 7.41)
Amisulpride	62.72 (53.92, 71.51)	7.04 (5.62, 8.46)
Haloperidol	62.22 (52.05, 72.39)	7.08 (5.46, 8.70)
Cariprazine	48.88 (45.35, 52.41)	9.28 (8.69, 9.87)
Lurasidone	45.22 (40.33, 50.11)	9.92 (9.01, 10.83)
Ziprasidone	44.54 (37.57, 51.51)	10.02 (8.82, 11.22)
Placebo	43.48 (37.51, 49.45)	10.20 (9.17, 11.23)
Lithium	41.52 (36.10, 46.94)	10.48 (9.52, 11.44)
Lumateperone	38.32 (31.95, 44.69)	11.02 (9.93, 12.11)
Zonisamide	33.90 (23.83, 43.97)	11.76 (10.05, 13.47)
Topiramate	27.78 (20.25, 35.31)	12.66 (11.52, 13.80)
Lamotrigine	25.40 (19.18, 31.61)	13.06 (12.04, 14.08)

Abbreviations: TC: total cholesterol; HDL: high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol; TG: total triglyceride; SUCRA: surface under the cumulative ranking curve; CI: credible interval.

Table 1: **Mean SUCRA and mean ranking based on data of fasting serum glucose, TC, TG, LDL, and body weight (presented as mean and 95% CI).**

mmol/L, compared to placebo]. Quetiapine ranked the last in elevating fasting serum glucose among the youths [SMD = –1.53 mmol/L, 95% CI = (–2.15, –0.91) mmol/L, compared to placebo], and ranked 2nd among the adults. Risperidone and valproic acid both tended to elevate insulin levels among the youths, while lurasidone ranked 1st in elevating insulin levels among the adults. Asenapine and lurasidone ranked the highest in elevating serum HbA1c among youths and adults, respectively. Lithium ranked higher than most of the interventions in elevating TC and TG levels among the youths. Risperidone was the most likely to affect serum prolactin levels among the youths, while olanzapine ranked 1st in elevating serum prolactin levels among the adults.

Current episode

Quetiapine ranked higher than placebo in elevating fasting serum glucose among patients with current episode of mania/hypomania or mixed state [SMD = 0.18 mmol/L, 95% CI = (0.06, 0.29) mmol/L], but ranked below placebo [SMD = –1.44 mmol/L, 95% CI = (–2.06, –0.83) mmol/L] among patients with current episode of bipolar depression. Lurasidone exhibited a similar effect with quetiapine on fasting serum glucose among manic patients [SMD = –0.14 mmol/L, 95% CI = (–0.30, 0.02) mmol/L], but ranked significantly higher than quetiapine among patients with bipolar depression [SMD = 1.53 pmol/L, 95% CI = (0.95, 2.11) pmol/L, compared to quetiapine]. Quetiapine ranked higher than lusaridone in elevating HbA1c levels among manic patients [SMD = 0.27%, 95% CI = (0.10, 0.44) %], which was contrary to bipolar depression [SMD = –0.59%, 95% CI = (–0.87, –0.32) %].

Sex ratio

Ziprasidone ranked 1st in elevating fasting serum glucose among trials with more female patients, while zonisamide ranked 1st among trials with more male patients. Lurasidone ranked higher than quetiapine in elevating insulin among trials with more female patients [SMD = 0.05 pmol/L, 95% CI = (–0.16, 0.25) pmol/L], which was contrary to the other subgroup [SMD = –0.08 pmol/L, 95% CI = (–0.62, 0.46) pmol/L], but both without statistical significance. Quetiapine exhibited similar effects with lurasidone in elevating TC levels among trials with more female patients, while it overcame lurasidone among trials with more male patients [SMD = 0.33 mmol/L, 95% CI = (0.03, 0.64) mmol/L].

Race

Olanzapine ranked 4th among trials with more white patients than non-white in elevating fasting serum glucose, but ranked below placebo among trials with more non-white patients [SMD = –0.12 mmol/L, 95% CI = (–0.69, 0.44) mmol/L]. Olanzapine also ranked 1st in elevating TC levels and ranked higher than most of the other interventions in elevating body weight in both subgroups.

Intervention duration

Risperidone ranked higher than the other interventions in elevating fasting serum glucose levels in the short-term subgroup [SMD = 0.56 mmol/L, 95% CI = (0.04, 1.07) mmol/L, compared to placebo], while lurasidone ranked significantly higher than risperidone in the long-term subgroup [SMD = 2.39 mmol/L, 95% CI = (1.63, 3.15) mmol/L]. Quetiapine overcame placebo in elevating insulin in the short-term subgroup [SMD = 0.33 pmol/L, 95% CI = (0.06, 0.61) pmol/L]. As for TC, quetiapine ranked 1st in the short-term group, but ranked 4th in the long-term subgroup. Amisulpride exhibited the most potent effects on body weight in the short-term subgroup. There was no RCT of long-term amisulpride, while quetiapine and olanzapine ranked significantly higher than most of the other interventions in elevating body weight in the long-term subgroup.

Baseline medication

Quetiapine ranked last in elevating fasting serum glucose levels among washed-out patients, while its ranking increased after eliminating sensitive trials. No significance was noticed among all comparisons in elevating insulin levels in the medication washed-out subgroup, while risperidone and valproic acid ranked significantly higher than most of the other interventions among patients with baseline medication. As for HbA1c, lurasidone [SMD = 0.26%, 95% CI = (0.06, 0.47)

%] and placebo [SMD = 0.21%, 95% CI = (0.04, 0.38) %] both ranked higher than quetiapine among washed-out patients, while quetiapine ranked higher than placebo among patients with baseline medication [SMD = 0.33%, 95% CI = (0.20, 0.45) %]. Olanzapine and risperidone affect TC levels and body weight the most.

League tables of subgroup analyses were summarised in Supplementary Appendix 6. The highlighted information of the analysing results was summarised in Table 2.

Discussion

In this NMA, 41 publications from 6 databases involving 11,678 participants and 17 individual pharmacological interventions were systematically reviewed, analysed, and summarised. This project further expanded previous work, while more evidence obtained through exhaustive and normative literature search puts deeper insights into the metabolic impact of commonly-used antipsychotics and mood stabilisers, and promotes rigorous comparisons of these drugs based on a comprehensive perspective.

Antipsychotics ranked generally higher than placebo and mood stabilisers in affecting metabolism, according to the analysing results. Second-generation antipsychotics including olanzapine, risperidone, and aripiprazole ranked the highest and most mood stabilisers ranked below placebo (Table 1), which is in accord with previous studies.[41–43] Analyses of efficacy and tolerability suggested that most antipsychotics reached therapeutic response within the observation duration, while olanzapine showed a higher dropout rate than placebo, which is mainly due to adverse events. The observed mood stabilisers were tolerable, but more evidence is in demand for evaluating their efficacy in treating BD.

Heterogeneity, which widens the range of 95% CI and makes the results ambiguous, is inevitable and observed according to the inconsistency checks and forest plots. Differences in the recruiting criteria, follow-up duration, daily dosage, and patient characteristics might be responsible, and heterogeneity in the patient characteristics could reflect the therapeutic difference among different populations. For example, a study allowed gradual doses of olanzapine raising and flexible dosing based on therapeutic response, which might conceal the potential adverse effects. Different consequences of fixed and flexible dosing have been addressed in the previous research,[44] but exploration of BD pharmacotherapies remains inadequate. Analysis of rate suggested that the studies responsible for high heterogeneity might be those applying quetiapine, olanzapine, ziprasidone, and aripiprazole. According to the primary publications, these trials recruited participants with underlying diseases or assisted medication, applied flexible daily dosage, or performed unfixed intervention duration, which is in accord with the above suppose. Differences in the baseline condition further influenced the tolerability of intervention (dropout rate), since patients in a morbid state might be more sensitive to adverse effects. Moreover, given the limited number of studies retrieved (N = 41), it was difficult to find out the specific sources responsible for heterogeneity, or the sources are too many and dispersive, so that each of them might count for a little that could not be selected via subgroup variables or sensitivity analysis. The small number of studies might also elevate the risk of unstable results. However, by reviewing previous literature and experience in clinical practice, the conclusions are still considered reliable.

Publication bias also existed since some of the funnel plots were asymmetric in overall and subgroup analyses (the fitted line leaned to one side). For example, some of the enrolled RCTs were phase III clinical trials with significant differences between the experimental and controlled groups, which are more likely to be exposed, especially those who applied newly-approved drugs such as lumateperone. Sensitivity checks were conducted to confirm the robustness. Apart from the studies assessed for high risk of bias, sensitivity was generated in the three-arm designed RCT carried out by Kowatch RA et al.,[45] in which the participants were all aged 3–7 years old. It is the only enrolled RCT recruiting children aged under 10 in this NMA. Since risperidone was reported to be more likely to affect metabolism among the youths than adults, it could be speculated that age probably contributed to sensitivity. Children might be more sensitive to the metabolic effects of risperidone. It was previously reported that second-generation antipsychotics led to weight gain rather than a deficit of glucose and lipid metabolism among children and adolescents with psychiatric disorders.[46,47] Nevertheless, after eliminating comparisons for high sensitivity and re-analysing the remaining data, few noteworthy changes were observed.

Olanzapine exhibited the highest risk of disturbing metabolism, according to Table 1. However, the underlying mechanisms associated with its therapeutic and metabolic effects have not been fully elucidated. A possible explanation is that olanzapine blocks dopamine D2 receptors and binds to the 5-HT2A, histamine 1, and muscarine 3 receptors, which are correlated to metabolic dysregulation.[48] Meanwhile, peripheral dopamine signaling might also be involved in the metabolic abnormality caused by dopamine receptor antagonists.[49] It was also demonstrated that most antipsychotics disturb glucose and lipid metabolism through intercellular signaling, epigenetic modification, and hepatoxicity,[18,50] resulting in increased sensitivity to obesity, diabetes, and cardiovascular disease.[18,51] Among patients with BD who were treated with lithium and valproic acid, elevated levels of adiponectin were detected, which is associated with obesity, diabetes, and dyslipidaemia.[52,53]

Classification	Highlighted information
Main outcomes	
Fasting serum glucose	1 16 interventions presented applicable data. 2 Primary ranking (1st, 2nd, 3rd, the last): risperidone, zonisamide, quetiapine, divalproex. 3 After sensitivity checks (1st, 2nd, 3rd, the last): risperidone, zonisamide, asenapine, divalproex. 4 Cariprazine ranked significantly higher than placebo.
Serum insulin	1 10 interventions presented applicable data. 2 Primary ranking (1st, 2nd, 3rd, the last): risperidone, valproic acid, ziprasidone, placebo. 3 After sensitivity checks (1st, 2nd, 3rd, the last): risperidone, valproic acid, lurasidone, placebo.
HbA1c	1 6 interventions presented applicable data. 2 Primary ranking (1st, 2nd, 3rd, the last): lurasidone, asenapine, quetiapine, topiramate. 3 After sensitivity checks (1st, 2nd, 3rd, the last): lurasidone, asenapine, ziprasidone, topiramate. 4 Comparison of lurasidone versus topiramate showed stable significance.
TC	1 17 interventions presented applicable data. 2 Primary ranking (1st, 2nd, 3rd, the last): risperidone, haloperidol, olanzapine, lamotrigine. 3 After sensitivity checks (1st, 2nd, 3rd, the last): olanzapine, risperidone, haloperidol, valproic acid. 4 Antipsychotics ranking below placebo were lurasidone, lumateperone, and cariprazine.
TG	1 17 interventions presented applicable data. 2 Primary ranking (1st, 2nd, 3rd, the last): olanzapine, haloperidol, asenapine, zonisamide. 3 After sensitivity checks (1st, 2nd, 3rd, the last): olanzapine, haloperidol, risperidone, zonisamide. 4 Mood stabilisers ranking higher than placebo were lithium, divalproex, and topiramate. 5 Antipsychotics ranking below placebo were lumateperone, lurasidone, and ziprasidone.
HDL (rank by the ability of reducing HDL levels)	1 16 interventions presented applicable data. 2 Primary ranking (1st, 2nd, 3rd, the last): quetiapine, cariprazine, valproic acid, divalproex. 3 After sensitivity checks (1st, 2nd, 3rd, the last): lamotrigine, olanzapine, quetiapine, aripiprazole.
LDL	1 17 interventions presented applicable data. 2 Primary ranking (1st, 2nd, 3rd, the last): haloperidol, asenapine, olanzapine, lamotrigine. 3 After sensitivity checks (1st, 2nd, 3rd, the last): olanzapine, haloperidol, placebo, topiramate.
Additional outcomes	
Body weight	1 17 interventions presented applicable data. 2 Primary ranking (1st, 2nd, 3rd, the last): amisulpride, quetiapine, olanzapine, topiramate. 3 After sensitivity checks (1st, 2nd, 3rd, the last): amisulpride, quetiapine, risperidone, topiramate. 4 Most of the head-to-head comparisons showed statistical significance.
BMI	1 13 interventions presented applicable data. 2 Primary ranking (1st, 2nd, 3rd, the last): olanzapine, amisulpride, risperidone, topiramate. 3 Rankings of the 1st, 2nd, 3rd, and the last kept consistent after sensitivity checks. 4 All interventions except for zonisamide ranked significantly higher than topiramate.
Waist circumference	1 9 interventions presented applicable data. 2 Rankings of the 1st, 2nd, 3rd, and the last: olanzapine, asenapine, cariprazine, zonisamide.
Serum prolactin	1 11 interventions presented applicable data. 2 Rankings of the 1st, 2nd, 3rd, and the last: risperidone, olanzapine, lurasidone, lumateperone. 3 Mood stabilisers ranked all below placebo.
Total serum bilirubin	1 5 interventions presented applicable data. 2 Only cariprazine ranked higher than placebo.
Subgroup analyses	
Age	1 Divalproex tended to elevate fasting serum glucose among the youths. 2 Quetiapine tended to elevate fasting serum glucose among the adults. 3 Lurasidone was likely to elevate serum insulin and HbA1c levels among the adults. 4 Lithium might affect serum TC and TG levels more among the youths than most of the other interventions. 5 Risperidone was likely to elevate serum prolactin levels among the youths. 6 Olanzapine tended to affect serum prolactin levels among adults.
Current episode	1 Quetiapine was more likely to affect fasting serum glucose among patients with bipolar mania. 2 Quetiapine ranked below lurasidone in elevating serum insulin levels among patients with bipolar mania 3 Quetiapine was more likely to elevate HbA1c levels than lurasidone among patients with bipolar mania 4 Lurasidone tended to affect fasting serum glucose more among patients with bipolar depression. 5 Lurasidone overcame quetiapine in elevating HbA1c levels among patients with bipolar depression.
Sex ratio	1 Ziprasidone tended to elevate fasting serum glucose among female patients. 2 Zonisamide was likely to elevate fasting serum glucose among male patients. 3 Lurasidone ranked higher than quetiapine in elevating serum insulin levels among female patients. 4 Quetiapine ranked higher than lurasidone in elevating serum insulin levels among male patients. 5 Quetiapine was more likely to elevate serum TC levels than lurasidone among male patients.

(Table 2 continues on next page)

Classification	Highlighted information
(Continued from previous page)	
Race	1 Olanzapine might perform stronger effect on fasting serum glucose among the white than the non-white.
Intervention duration	1 Risperidone was likely to elevate fasting serum glucose when applied for no more than 6 weeks. 2 Lurasidone probably overcame risperidone in elevating fasting serum glucose when applied for over 6 weeks. 3 Quetiapine tended to elevate serum TC levels when applied for no more than 6 weeks. 4 Quetiapine tended to elevate body weight when applied for over 6 weeks.
Baseline medication	1 Quetiapine was unlikely to affect fasting serum glucose among the medication washed-out. 2 Quetiapine tended to elevate HbA1c levels among patients with baseline medication. 3 Risperidone and valproic acid affected serum insulin levels to the most among patients with baseline medication.

Abbreviations: TC: total cholesterol; HDL: high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol; TG: total triglyceride; HbA1c: hemoglobin A1c; BMI: body mass index.

Table 2: **Highlighted information on the general and subgroup analyses.**

However, the metabolic effects of mood stabilisers might be presented indirectly. For example, lithium inhibits thyroid function, which in turn leads to obesity.[54] Increased serum levels of leptin were also noted in patients who received lithium therapy and gained body weight,[55] which was later addressed with genetic variation at the leptin gene locus.[56]

The role of bilirubin metabolism in the pharmacological process of antipsychotics and mood stabilisers has not been fully elucidated. Previous studies showed that antioxidant properties of bilirubin to counteract oxidative stress might be correlated with the positive symptoms of schizophrenia,[57] and serum direct bilirubin levels were associated with the onset of abdominal obesity among schizophrenia patients.[58] Antipsychotics elevate serum prolactin via their affinity for dopamine D2 receptors and the ability to cross the blood–brain barrier.[59] It is noted that the population with psychosis hypersensitivity but never acquired antipsychotics also showed elevated serum prolactin levels, indicating the potential for changes in the levels of prolactin as emerging biomarkers for psychosis onset.[59] Few studies of prolactin focused on mood stabilisers. Existing evidence announced little effect of lithium on serum prolactin,[60] and GABA circuit activating agents such as valproic acid could reduce basal prolactin secretion.[61] In addition, topiramate also activates GABAergic neurons and antagonises α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate glutamate receptors, resulting in the inhibition of prolactin release, suggesting it as a potential adjunctive therapy for antipsychotics-induced hyperprolactinemia.[62]

Results of the subgroup focus on lumateperone, a recently on-the-market second-generation antipsychotics acting as a neurotransmitter system regulatory agent[63] which performed efficacy in symptom and cognition improvement among patients with schizophrenia.[64] Lumateperone demonstrates a higher affinity for dopamine D2 receptors,[65] and its robust and dose-dependent partial agonist activity for dopamine D2 receptor reduces the risk of excessive dopamine blockade-related side effects and normalises dopamine neurotransmission in the mesolimbic and mesocortical regions.[65,66] Previous trials have highlighted the intriguing efficacy of lumateperone in treating bipolar depression,[67,68] as well as a lower rate of developing metabolic syndrome,[69,70] which might be correlated with its minimal binding to histaminergic or muscarinic receptors.[70] However, due to the inadequate evidence of its clinical applicability and trials applying lumateperone for treating bipolar mania, larger cohorts with strict blindness and randomness require more practical and reliable clinical guidelines.

The stabilizing effect on fasting serum glucose of lurasidone has been previously observed, with a recommendation as an alternative for patients with BD and diabetes or other drug-induced metabolic issues.[71,72] Mild decrease in fasting serum glucose was also recently detected to be correlated with symptom improvement among patients with BD who received lurasidone treatment.[73] However, few studies focused on the difference in mood states, which was addressed in this NMA. The changeable mood states of BD are correlated to glucose metabolism, since activating *SIRT-1*, a gene regulating glucose uptake and insulin signaling,[74] helped improve bipolar depression.[75] Significantly lower ratio of glucose metabolic rates was detected in the left dorsal anterolateral prefrontal cortex divided by the rate for the ipsilateral hemisphere in patients with bipolar depression.[76] Meanwhile, neuroimaging and pharmacological studies on the "switch" mechanism of BD addressed the periodic functional changes in brain regions such as the temporal cortex, frontal-striatal-thalamic, and default-mode network regions for mood state switching.[77] In consideration of the evidence that bipolar depression is associated with insulin resistance and sensitivity of developing hyperglycemia,[78] it can be speculated that linked glucose metabolic deficits in specific brain regions might be responsible for the apparent metabolic disorder induced by lurasidone in bipolar depression.

Another emerging finding concentrates on quetiapine. When co-intervention at the baseline existed, quetiapine showed a more vital ability to affect glucose

metabolism than other interventions. Pharmacokinetic and pharmacodynamics drug–drug interactions might be responsible,[79] but further evidence of the specific role of different baseline medications is still in demand. Mood stabilisers such as valproic acid[80] and divalproex,[81] as well as antidepressants such as fluoxetine[82] may be appropriate breaking points, since combined treatment of antipsychotics and mood stabilisers are usually applied on patients with BD, and patients with atypical BD are easily misdiagnosed as unipolar depression and treated with antidepressants.[83] Moreover, quetiapine seemed to affect metabolism more among adults than children and adolescents according to results of subgroup analyses, which is in accord with a previous systematic review.[84] However, RCT-based evidence on the metabolic effects of quetiapine among patients with BD is still insufficient for building reliable clinical guidelines.

As for the between-subgroup difference of age, quetiapine, divalproex, and lithium ranked differently among adults and youth, possibly due to differences in metabolism and hormone levels. Irritability and hyperactivity occur more in adolescent bipolar mania, and adolescent patients with BD show a higher rate of comorbid psychiatric disorders than adult patients,[85] which might explain the difference. In addition, it was estimated that children and adolescents receiving antipsychotics performed a higher risk of developing extrapyramidal symptoms, hyperprolactinemia, and metabolic syndrome,[86,87] which put forward issues of pharmacotherapy safety among the youth. According to existing policies, quetiapine is recommended by the Food and Drug Administration of the US for patients aged 10 years or older with acute bipolar mania or mixed state, while valproic acid has not been approved for adolescent BD pharmacotherapy.[85] Second-generation antipsychotics including risperidone and olanzapine have been approved for adolescent acute bipolar mania,[85] although evidence suggests that they are more likely to cause metabolic disturbance among the youth than the grown-up.[88] Moreover, previous studies showed that children might be more sensitive to drug-induced weight gain (or increase of BMI and waist circumference), rather than a disturbance of glucose and lipid metabolism,[47,89] which might be due to differences in the gut microbiome.[90] Moreover, little evidence was found among the senior patients which might be due to the relatively low prevalence rate. However, such information is also attention-gathering since chronic metabolic deficits such as diabetes might lead to the increased rate of mortality,[91] and more trials targeting different age groups are needed to map the age-based metabolic effects of antipsychotics and mood stabilisers.

Sex differences in the metabolic effects of antipsychotics and mood stabilisers might be due to differences in body fat percentage, levels of the hormone, volume of the amygdala,[92] and gene polymorphism, in which *CYP1A2* and *DRD3* attracted the most attention for their influence on the blood concentration and clearance of quetiapine.[93] Previous studies reported that the rate of metabolic syndrome after antipsychotic intervention among female patients was 51.6%, which was significantly higher than among male patients (36.0%).[94,95] Possible explanation for race difference might exist in the expression of enzymes in the cytochrome P450 system, which acts as an essential pathway for the metabolism of antipsychotics.[96] It was found that olanzapine did not disturb fasting serum glucose and HDL among white participants, while it affected these two indicators among black/Hispanic participants.[97] Although detailed distinction of age, sex, and race subgroup was not carried out due to the overlap of these demographic indicators among different studies, inspiration for medication safety was released from the analysing results.

One more concern is clinical practicability. Although pooled results of mean SUCRA and ranking were provided, the weight difference of these interventions should be taken into consideration when making clinical decisions. For example, patients with underlying cardiovascular diseases may pay more attention to lipid parameters, while diabetes patients focus more on glucose metabolism. It should also be noted that the evidence-based information is worth considering despite the difference between the ranking results and existing clinical guidelines. Recommendations of existing handbooks or guidelines hardly prefer the drugs ranked anteriorly in this NMA such as lumateperone and zonisamide as first-line medication for BD.[85] Possible explanations might be the efficacy, tolerability, acceptance, and safety, since patients of different races or social environments might response differently. The Food and Drug Administration of the US approved lumateperone for schizophrenia early in 2019, but lumateperone was not yet available in China until 2022. Meanwhile, price, adverse effect, onset time, and time of maintenance all need to be taken into consideration in clinical practice. In addition, most of the head-to-head comparisons presented in the league tables showed little significance, which might be due to actual similarity or the small number of included studies that concealed possible relevance. Nevertheless, the results were still considered noteworthy, since the ranking and difference between different subgroups provided information for clinical decision and drug compatibility.

There are several limitations in this NMA. First, the number of enrolled studies is quite limited. Since only 41 RCTs were included in the analysis, occasionality could not be ruled out. Second, sensitivity checks were based on the elimination of the studies or comparisons assessed with a high risk of bias, which contributed to the subjectivity of the checking results. Another caveat is that this NMA provides ranking results mainly from the perspective of affecting metabolism, but does not

further consider their therapeutic effects. Moreover, since the underlying mechanisms of the metabolic effects of newly-approved antipsychotics and most mood stabilisers are largely unknown, the practicability of the results needs to be proved by further research evidence.

In future studies, large-cohort trials and comprehensive analyses are needed for a combined evaluation of the efficacy, tolerability, acceptability, as well as short- and long-term adverse effects of antipsychotics and mood stabilisers. Research focusing on drug metabolism, biotransformation, and interactions is also in demand for elucidating the mechanism of BD and setting up standardised clinical guidelines.

Despite the existing limitations, this NMA puts forward clinical inspersions for patients with BD, psychiatric clinicians, guideline developers, and policymakers to optimise the selection and compatibility of antipsychotics and mood stabilisers.

In conclusion, the results indicate that 1) Antipsychotics are more likely to affect metabolism than mood stabilisers, among which olanzapine generally ranks the highest, with lamotrigine ranking the lowest; 2) Most antipsychotics perform a higher rate of response and remission than placebo, and are also tolerable except for olanzapine; 3) Quetiapine is more likely to affect glucose metabolism among male adults with a current episode of bipolar mania/hypomania, or mixed state and with baseline medication, while long-term lurasidone tends to affect glucose metabolism among female patients with bipolar depression; 4) Among the youths, divalproex tends to affect glucose metabolism, while lithium shows stronger influence on lipid metabolism; 5) Lumateperone might be an alternative for bipolar depression.

Contributors

LZK and HZW carried out literature identification, selection, and review, did data extraction and analyses, prepared figures, and wrote the paper; NY and CYX did literature selection and review, data extraction, and wrote the paper; YQC and YYZ did data extraction, prepared figures, and polished the paper; XNG sorted out the supplementary materials and polished the paper; JL conceptualised and edited the paper; SHH confirmed the results of data collection, conceptualised, and edited the paper. All authors read and approved the final manuscript.

All authors confirmed that they had full access to all the data in the study and accepted responsibility for the decision to submit for publication, and all authors (LZK, HZW, NY, CYX, YQC, YYZ, XNG, JL, and SHH) have verified the underlying data.

Data sharing statement

All data in this study are available upon request by contact with the corresponding author.

Declaration of interests

No conflicts of interest, financial or otherwise, are declared by the authors. All authors were not paid to write this article by a pharmaceutical company or other agency.

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Appendix A. Supplementary data

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