Comparative efficacy and safety of 4 atypical antipsychotics augmentation treatment for major depressive disorder in adults: a systematic review and network meta-analysis

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Abstract

Background: Atypical antipsychotic (AAP) augmentation is an alternative strategy for patients with major depressive disorder (MDD) who had an inadequate response to antidepressant therapy. We aimed to compare and rank the efficacy and safety of 4 AAPs in the adjuvant treatment of MDD. Methods: We searched randomized controlled trials (RCTs) published and unpublished from the date of databases and clinical trial websites inception to April 30, 2022. The risk of bias and certainty of the evidence is assessed using the Cochrane bias risk tool and GRADE framework, respectively. Based on the random effects model, we estimated summary risk ratios (RRs) or standardized mean difference (SMD) using network meta-analysis. This study is registered with PROSPERO, number CRD42012002291. Results: 57 eligible RCTs comprising 10900 participants were included. In terms of primary efficacy outcome, compared with placebo, all AAPs had significant efficacy (SMD = -0.40; 95% CI, -0.68 to -0.12 for quetiapine; -0.35, -0.59 to -0.11 for olanzapine; -0.28, -0.47 to -0.09 for aripiprazole and -0.25, -0.42 to -0.07 for brexpiprazole, respectively). In terms of acceptability, no significant difference was found, either agents versus agents or agents versus placebo. In terms of tolerability, compared with the placebo, quetiapine (RR = 0.24; 95% CI, 0.11-0.53), olanzapine (0.30,0.10-0.55), aripiprazole (0.39,0.22-0.69), and brexpiprazole (0.37,0.18-0.75) were significantly less well tolerated. 8 (14.2%) of 56 trials were assessed as low risk of bias (RoB), 38 (67.9%) trials had moderate RoB, and 10 (17.9%) had high RoB; In accordance with the GRADE, the certainty of most evidence was low or very low. Limitations: The overall quality of evidence is low, and the long-term benefits of AAPs are unclear. Conclusion: Adjuvant AAPs had significant efficacy compared with placebo, but treatment decisions need to be made to balance the risks and benefits.

1. Introduction

Major depressive disorder (MDD) is one of the most common, chronic, and burdensome psychiatric disorders. It affects approximately 6% of the adult population worldwide each year (Bromet et al, 2011). The prevalence of MDD is twice as high in women as in men (Seedat et al, 2009) and higher in high-income countries than in low-income countries (Kessler & Bromet, 2013). MDD is a debilitating disease that is characterized by depressed mood, diminished interests, impaired cognitive function, and vegetative symptoms, which is the major leading contributor to chronic disease burden and disability (Global Burden of Disease Study 2013 Collaborators, 2015; Otte et al, 2016). Compared with the general population, patients with MDD have a higher suicide mortality rate (Chesney et al, 2014a; Flint & Kendler, 2014). The vast majority of suicides occur during a depressive episode (Chesney et al, 2014b). Furthermore, some studies indicated that MDD increased the incidence rate of some basic diseases, such as hypertension, diabetes, and cognitive impairment (Bw et al, 2013). However, a large proportion of patients with MDD did not receive proper treatment, especially in low-income countries (Ten Have et al, 2013; Wang et al, 2007).

Management of MDD primarily comprises psychotherapy and pharmacological treatment (Fava & Kendler,
Regarding pharmacological treatment, selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) are currently still the first-line antidepressants. First-line psychological treatment recommendations for acute MDD include cognitive-behavioral therapy, interpersonal therapy, and behavioral activation (BA) (Parikh et al., 2016). In addition, with further study of the pathogenesis of depression, a variety of types of compounds, including anti-inflammatory agents (Bai et al., 2020), glutamatergic system modulators (Sanacora et al., 2008) and neurokinin 1 antagonists (Ratti et al., 2013), play an definite role in the treatment of MDD.

Despite a wide variety of pharmacological and non-pharmacological treatments available for MDD, nearly 30% of patients did not experience remission (Rush et al., 2006a). A study (Ciprian et al., 2009) had shown that all monoamine-based antidepressants, regardless of their pharmacological category, were only 50% effective. This inadequate response to conventional antidepressant therapy has been termed treatment-resistant depression (TRD). Augmentation strategies refer to the addition of another type of medication to an existing antidepressant to enhance efficacy, which can be used in patients with inadequate response to a single antidepressant. Multiple guidelines (Kennedy et al., 2016; Gelenberg et al., 2010; Bauer et al., 2017) recommend AAP augmentation strategies for patients with an inadequate response to antidepressant therapy. To date, a total of 4 AAPs has been approved by the U.S. Food and Drug Administration (FDA) for the adjunctive treatment of MDD, namely olanzapine/fluoxetine combination (OFC), aripiprazole, quetiapine extended-release (quetiapine XR), and brexpiprazole. According to a previous meta-analysis, atypical antipsychotics effectively augmentation antidepressants in MDD (Nelson & Papakostas, 2009). Due to the lack of head-to-head comparisons between atypical antipsychotics, it is impossible to directly assess their differences in efficacy. However, network meta-analysis of existing randomized controlled trials (RCTs) made it possible to compare AAPs comprehensively and to understand the merits and disadvantages of the multiple interventions (Higgins & Welton, 2015). Previous studies (Nuñez et al., 2022; Yan et al., 2022b; Zhou et al., 2015) utilizing NMA approaches investigated the efficacy, acceptability and tolerability of AAPs in the treatment of TRD. However, our study differs from previous studies. First, we included not only patients with treatment-resistant depression but also patients with non-treatment-resistant major depression. Secondly, in terms of electronic database, besides the commonly used English database, we also included the Chinese database to increase the recall rate. Third, we focused on the short-term efficacy of AAPs, with 8-week data predominant and 4-to 12-week data included if not available. Therefore, we aimed to do a systematic review and network meta-analysis to compare and rank 4 atypical antipsychotics adjunctive antidepressants for treating adults with a unipolar major depressive disorder to provide guidance and reference for the selecting of clinical practice.

2. Methods

2.1 Search strategy and eligibility criteria

According to PRISMA statement guidelines (Page et al., 2021), we did a systematic review and network meta-analysis of placebo-controlled and head-to-head RCTs that compared an adjunctive atypical antipsychotic to another class of adjunctive atypical antipsychotics or placebo. The PRISMA checklist is shown in Supplementary Appendix 1. This study is registered with PROSPERO, number CRD42022346207.

In this network meta-analysis, we searched PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (WOS), Embase, PsycINFO, and China National Knowledge Infrastructure (CNKI), Wan Fang database, VIP database, China Biology Medicine (CBM) database for RCTs published from the date of database inception to April 30, 2022, comparing atypical antipsychotics with another atypical antipsychotic or placebo augmenting the action of antidepressants in adults of both sexes) with a primary diagnosis of major depressive disorder according to standard operationalized diagnostic criteria (Research Diagnostic Criteria, Diagnostic and Statistical Manual for Mental Disorders, fourth edition (DSM-IV); Chinese Classification and Diagnostic Criteria for Mental Disorders, 3rd Edition (CCMD-3); the Diagnostic and Statistical Manual for Mental Disorders, fourth edition, text revision (DSM-IV-TR); the Diagnostic or Statistical Manual for Mental Disorders, fifth edition (DSM-5) and International Statistical Classification of Disease and Related Health Problems (ICD-10)). Meanwhile, to locate unpub-
lished literature, we also searched ClinicalTrail.gov for data supplementation with unpublished or ongoing RCTs. No language restrictions were applied. Each database takes medical subject headings (MeSH) and Text words to search. Take the PubMed database as an example. Details of the database searching process are shown in Supplementary Appendix 2.

Exclusion criteria were: (1) Studies including patients with bipolar depressive disorder or psychotic features (2) Case reports, reviews, protocols, meeting, letters, editorials, or retrospective studies were excluded. (3) Randomised trials without a placebo or atypical antipsychotic.

2.2 Data extraction

Data were extracted independently by three investigators (WWL, MTL, HBW) using data extraction forms. Disagreements will be resolved by an experienced researcher (ZKQ) when needed. A data extraction form was completed by using Excel 2010 literature data extraction table. We obtained the following information from each study: the first author’s surname, publication year, study period, mean ages of participants, percentage of female participants and number of participants in each group, description of the intervention, diagnostic Criteria, methods for measuring depression severity, sponsored (commercial industries (CI), non-profit organizations (NPO), unclear). We contacted the authors for further information when data was insufficient or missing.

2.3 Quality assessment

We assessed the studies’ risk of bias following the Cochrane Handbook for Systematic Reviews of Interventions. The bias risk for these studies was assessed based on the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The risk of bias was classified into high, unclear, or low. The included trials were graded as low, moderate or high quality based on the following criteria (Bai et al, 2020): (1) trials were considered high quality when both randomisation and allocation concealment were assessed as a low risk of bias and all other items were assessed as low or unclear risk of bias in a trial; (2) a trial was judged to be of low quality when one or more of the seven assessment domains for risk of bias were considered high risk of bias; (3) trials were considered moderate quality if they met neither the criteria for high nor low risk. Additionally, The certainty of evidence produced by the synthesis for the primary outcome was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework (Salanti et al, 2014). Each network estimate of primary outcomes according to the criteria: risk of bias, indirectness, inconsistency, imprecision, and publication bias were assessed. Comparison-adjusted funnel plots were used to evaluate publication bias in the network meta-analysis (Salanti et al, 2011). We downgraded the evidence by one level if a domain was rated as “serious” and by two levels if a domain was rated as “very serious”. In the end, an overall judgment of the certainty of the evidence was derived by assigning to each comparison an overall qualitative judgment based on four levels of evidence: high, moderate, low, and very low.

2.4 Outcomes measures and definitions

The primary efficacy outcome is depressive symptom score (the mean change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to endpoint). The primary safety outcomes are acceptability (all-cause discontinuation, defined as the percentage of patients who terminated the study for any reason) and tolerability (side-effects discontinuation, defined as the percentage of patients who terminated the study for adverse effects). The secondary efficacy outcome were response rate and remission rate. The response to treatment was defined as at least 50% reduction from baseline in depression scales (MADRS or HAMD). Remission was defined as at least 75% reduction from baseline in depression scales or HAMD [7] (MADRS [7]) at the endpoint. Finally, we measured the change chance in Hamilton Depression Scale (HAMD) total score from baseline to endpoint and the incidence of adverse events (adverse events incidence rate).

2.5 Statistical analyses
Based on the random effects model, we used STATA/MP (version 16) for data analysis. In the network meta-analysis, the effect size for dichotomous outcomes was the risk ratio (RR) and its 95% confidence intervals (CIs). Furthermore, because different overall MDD symptomatology rating scales were used, the effect size measure for continuous outcomes was the standardized mean difference (SMD) and its 95% CIs. Based on the frequentist framework, we performed a network meta-analysis to compare the efficacy and safety of different atypical antipsychotics. We assessed statistical heterogeneity in each pairwise comparison using Cochrane’s Q test and I² statistics. For the Q test, a p-value <0.10 was considered to indicate significant heterogeneity, while for I², a value of I² = 0% to 50% was considered as low heterogeneity; 50% to 75% as moderate heterogeneity; and 75% to 90% as high heterogeneity (Higgins et al, 2003). STATA/MP (Version 16) was used to generate a network evidence plot for each outcome (Chaimani & Salanti, 2015). When a closed loop (direct and indirect evidence coexist) appears in the network evidence plot, we evaluated consistency statistically using the design-by-treatment test (Dias et al, 2010a). We performed effect size synthesis under the consistency model when p-value > 0.05 and under the inconsistency model when p-value < 0.05. The statistic inconsistency was assessed using global and local approaches to evaluate the inconsistency between direct and indirect evidence (Chaimani et al, 2013). Furthermore, the node-splitting method (Dias et al, 2010b) estimates direct and indirect treatment effects and their difference. To rank the treatments for each outcome, we used the surface under the cumulative ranking curve (SUCRA) (Salanti et al, 2011). Finally, we performed some sensitivity analyses of the conclusions for two primary outcomes (primary efficacy outcome and acceptability) according to the following variables: (1) patients with TRD (including Only studies with at least one inadequate response to conventional antidepressant therapy); (2) High quality study (excluding studies with a high risk of bias); (3) Large sample study (excluding studies with a sample size of less than 30).

3 Results

3.1 Search results and study characteristics

The search identified 2284 records through the database searching and the Clinical Trials Registry Platform. The retrieval details are as follows, PubMed (164), WOS (458), Embase (621), CENTRAL (576), CNKI database (41), Wan Fang data (212), CBM database (41), PsycINFO (53), Clinical Trail. gov (52) and VIP database (118). After deduplication of the retrieved clinical trials, 1597 studies were obtained. Then 153 full-text articles were retrieved based on their titles and abstracts. Overall, 56 RCTs (comprising 11,448 patients) met the inclusion criteria for systematic review and network analysis. The specific details of the PRISAM flow chart are shown in Figure 1.

56 studies were included in the network meta-analysis for the quantitative synthesis study. The studies included in the network analysis had the following characteristics: The mean study sample size was 189 participants; All of the participants had a mean age of 42.34 years [standard deviation (SD) 8.68], and the proportion of females was 54%. The duration of trials was 7.29 weeks, ranging from 4 to 12 weeks.; Baseline severity scores in patients with MDD were reported in 34 (60%) of 56 studies and the overall mean baseline score at study entry was 30.37 (SD 5.37). 21 (38%) of 56 were multi-Centre studies and the rest were single-Centre studies; Of the 56 studies, 19 declared a sponsorship from commercial industries (CIs), and 34 did not declare whether to accept sponsorship; In most studies, the diagnostic criteria for major depressive disorder were DSM-IV-TR. The details of study characteristics were presented in Table 1. The number of studies and patients with each outcome are presented in supplementary Appendix 3.
Figure 1. Flowchart of the study selection

Table 1. Characteristics of included studies

Table 1. (Continued)

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Abbreviations: 1. Outcome Measurement: Score changes from baseline to endpoint (MADRS) Response rate ([?]50% reduction in HAMD or MADRS) Remission rate (HAMD [?]7 in endpoint or (total score [?]10 and [?]50% reduction in MADRS)) Dropouts for any reason Dropouts for Adverse events Adverse events rate Score changes from baseline to endpoint (HAMD-17). 2. OFC: olanzapine/fluoxetine combination 3. FLC: fluoxetine 4. ADT: antidepressant therapy 5. MADRS: Montgomery-Asberg Depression Rating Scale 6. HAMD: Hamilton Rating Scale for Depression 7. CIs: commercial industries 8. NA: no available

3.2 Quality assessment of included study

The studies’ risk of bias was assessed following the Cochrane Handbook for Systematic Reviews of Interventions. A total of 56 studies were RCTs, however, only 37 described the randomization method. 48(85.7%) studies did not report allocation concealment. The percentage of studies with high, unclear, and low risk of bias for the rest 5 domains was: 37.7%, 60.3%, and 2.0% for blinding of patients and personnel, 5.6%, 92.4%, and 2.0% for blader blinding, 26.4%, 56.6%, and 17.0% for missing outcomes, 35.8%, 64.2%, and 0% for selective reporting, and 0%, 100%, and 0% for other biases. According to the criteria, 8(14.2%) studies...
were evaluated as high quality, 38 (67.9%) studies were of moderate quality while 10 (17.9%) studies were of low quality. The quality of studies included in the network meta-analysis was generally low. The risk of bias graph and risk of bias summary are reported respectively in

**Supplementary Appendix 4.**

According to GRADE, the quality of evidence for response rate and adverse events rate was rated as low overall. Detailed quality of evidence assessment was shown in

**Supplementary Appendix 5.**

According to the result of the heterogeneity assessment in each comparison. In terms of primary efficacy outcome, except aripiprazole augmentation group ($I^2=0\%$), the other groups have different degrees of heterogeneity, and the specific value is ($I^2=33\%$ for brexpiprazole augmentation group; $74\%$ for OFC; $92\%$ for quetiapine); In terms of acceptability, brexpiprazole augmentation group ($I^2=92\%$) was considered as high heterogeneity, other Groups was low heterogeneity; In terms of tolerability, all group were considered as low heterogeneity. Detailed results, including primary and secondary outcomes, were given in **Supplementary Appendix 6.**

The test of global inconsistency showed that no significant difference was present between the consistency and inconsistency models in terms of primary efficacy outcome ($P=0.417$), acceptability ($P=0.554$) and tolerability ($P=0.203$). The results of Local inconsistency (loop-specific) for all outcomes indicated that inconsistency was not significant. The result of inconsistency from the node-splitting model showed no significant differences in primary efficacy and safety (**Supplementary Appendix 7**).

The comparison-adjusted funnel plots of the network meta-analysis for primary outcomes did not indicate any publication bias (**Supplementary Appendix 8**).

### 3.3 Results of network meta-analysis

**Figure 2** shows the network plots of eligible comparisons for 7 outcomes (depressive symptom score (MADRS), acceptability, tolerability, response rate, remission rate, adverse events incidence rate, depressive symptom score (HAMD)). All AAPs had at least one placebo-controlled trial. Except for the depressive symptom score (HAMD), the remaining 6 outcomes had a closed loop (brexpiprazole vs quetiapine vs placebo).

#### 3.3.1 Efficacy outcomes

The results of depressive symptom score (MADRS) and response rate from the network meta-analysis are presented in Figure 3. In terms of primary efficacy outcome, A total of 23 studies (comprising 4 AAPs) were included in the primary efficacy analysis [depressive symptom score (MADRS)]. Compared with the placebo, quetiapine (SMD= -0.40; 95% CI, -0.68 to -0.12), olanzapine (SMD= -0.35; 95% CI, -0.59 to -0.11), aripiprazole (SMD= -0.28; 95% CI, -0.47 to -0.09), and brexpiprazole (SMD = -0.25; 95% CI, -0.42 to -0.07) were significantly more effective. However, there was no significant difference in efficacy among the AAPs.

In terms of response rate. Compared with the placebo, a significant increase was found in all APPs. In comparison among AAPs, aripiprazole was associated with a higher response rate than olanzapine (RR 1.22, 95%CI 1.07–1.40), quetiapine (RR 0.76, 95% CI 0.66–0.88) were less efficacious than aripiprazole.

**Figure 3. Network Meta-Analysis of Depression symptom score(MADRS) and Response rate**


**Abbreviations:** SMD= standardized mean difference; CI= confidence interval; BRE: brexpiprazole; ARI: aripiprazole; OLA: olanzapine; QTP: quetiapine; PBO: placebo. To obtain RRs for comparisons in the
opposite direction, reciprocals should be taken. The significant results were bolded and tilted.

### 3.3.2 safety outcomes

The results of acceptability and tolerability from the network meta-analysis are presented in Figure 4. In terms of acceptability, 20 studies (comprising 7,524 patients) were included in the acceptability analysis, no significant difference was found in 4 AAPs than placebo. In terms of tolerability, a total of 20 studies (comprising 6,524 patients) were included in the tolerability analysis. Compared with the placebo, quetiapine (RR= 0.24; 95% CI.0.11-0.53), olanzapine (RR= 0.30; 95% CI. 0.10-0.55), aripiprazole (RR= 0.39; 95% CI.0.22-0.69), and brexpiprazole (RR = 0.37; 95% CI. 0.18-0.75) were significantly less well tolerated. Unfortunately, no significant difference in safety was found among 4 AAPs. The rest outcomes results of network meta-analyses are given in Supplementary Appendix 9.

Figure 4. Network Meta-Analysis of Acceptability and Tolerability

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**Abbreviations:** RR=risk ratio; CI=confidence interval; BRE: brexpiprazole; ARI: aripiprazole; OLA: olanzapine; QTP: quetiapine; PBO: placebo. To obtain RRs for comparisons in the opposite direction, reciprocals should be taken. The significant results were bolded and tilted.

Based on cumulative probability plots and SUCRAs, table 2 and figure 5 showed the ranking of medications of 7 outcomes. The ranking for MDD patients of primary efficacy outcome from high to low was as follows: quetiapine, olanzapine, aripiprazole, brexpiprazole, and placebo. In terms of acceptability, each treatment group was ranked brexpiprazole, placebo, olanzapine, aripiprazole, and quetiapine from largest to smallest. In terms of tolerability, each treatment group was ranked placebo, aripiprazole, brexpiprazole, olanzapine, and quetiapine from largest to smallest. In addition, in terms of response rate and remission rate, aripiprazole ranked first.

**Table 2. SUCRA Probability ranking of outcome indicators.**

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**Abbreviations:** BRE: brexpiprazole; ARI: aripiprazole; OLA: olanzapine; QTP: quetiapine; PBO: placebo; ADT: antidepressant therapy

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**Figure 5. The ranking of TCMIs based on cumulative probability plots and SUCRA.**

a (depressive symptom score (MADRS)), b (all-cause discontinuation), c (side-effect discontinuation), d (remission rate), e (adverse events incidence rate), f (response rate), g (depressive symptom score (HAMD)).

### 3.4 Sensitivity analysis of the primary outcome

Sensitivity analyses of the primary efficacy and acceptability outcomes were performed in three domains(1) patients with TRD (including only studies with at least one inadequate response to conventional antidepressant therapy); (2) High quality study (excluding studies with a high risk of bias); (3) Large sample study
(excluding studies with a sample size of less than 30). The results of three sensitivity analyses were robust. The sensitivity analyses results for primary efficacy and acceptability outcomes were presented in Supplementary Appendix 10.

4. Discussion

Based on 56 studies comprising 57 RCTs, this network meta-analysis examined the efficacy and safety of atypical antipsychotics as adjunctive treatment in patients with a unipolar major depressive disorder. 4 atypical antipsychotics (olanzapine/fluoxetine combination(OFC), aripiprazole, quetiapine, and brexpiprazole) approved by the U.S. FDA for adjunctive treatment of MDD were included.

In terms of primary efficacy outcome, all atypical antipsychotics showed significant efficacy compared with placebo, but no significant differences were found among atypical antipsychotics. In terms of acceptability, no significant difference was found between AAPs and placebo. In terms of tolerability, 4 AAPs were significantly less well tolerated. However, no significant difference in acceptability or tolerability was found among 4 AAPs. In terms of response rate, compared with placebo, all atypical antipsychotics significantly increased response rate. In addition, aripiprazole was superior to quetiapine and olanzapine among atypical antipsychotics. In terms of incidence of adverse events, except for olanzapine, the incidence of other AAPs adverse events was significantly higher than that with placebo. In summary, all AAPs were superior to placebo in reducing depression scores and improving remission rates, which is consistent with previous studies (Núñez et al., 2022; Zhou et al., 2015). This study further validates the effectiveness of adjunctive atypical antipsychotics in the treatment of MDD. Meanwhile, this result is consistent with guidelines for adjunctive AAPs for MDD as a first-line treatment after inadequate response to antidepressants.

Regarding the literature’s quality assessment, most studies were unclear or at high risk of bias. Many of the Chinese RCTs included in this study were rated as moderate risk due to lack of detailed description of randomization, allocation, and blinding, which contributed to the overall low quality of the studies. According to GRADE, the quality of evidence for primary outcomes was rated as very low or low overall. The results of sensitivity analysis (including only studies with a diagnosis of TRD, excluding studies with small sample size, and excluding studies with high risk) were robust.

Aripiprazole ranked first in improving response and remission rates and second in reducing depression scores (HAMD scales) from baseline to endpoint. Aripiprazole is the first atypical antipsychotic drug approved by the U.S. FDA for the adjunctive treatment of MDD. Furthermore, aripiprazole is a primary recommendation for inadequate response to antidepressant therapy (Kennedy et al., 2016). Adjunctive aripiprazole has significant clinical benefits compared with placebo. In terms of tolerability, aripiprazole augmentation did not produce more discontinuations due to adverse events than placebo. Compared with other AAPs, aripiprazole was better but not significantly different. Overall, aripiprazole had higher efficacy and better tolerability among atypical antipsychotics. Aripiprazole’s pharmacology—characterized by its unique agonist activity at dopamine D₂, D₃ and serotonin 5-HT₁A receptors as well as antagonist activity at serotonin 5-HT₂A receptors (Casey & Canal, 2017). Unfortunately, aripiprazole augmentation had significantly higher rates of adverse events than placebo. The most common adverse events with aripiprazole (Berman et al., 2011; Nelson & Papakostas, 2009; Selfani et al., 2017) included akathisia, fatigue, and weight gain, which may account for the higher rate of adverse events in the aripiprazole augmentation group.

Quetiapine was approved for the adjunctive treatment of MDD in several countries worldwide, including the European Union, Canada, the United States, and Australia. The role of quetiapine has been demonstrated in patients with treatment-resistant depression, either as monotherapy or as augmentation therapy (Chen et al., 2011; Ignácio et al., 2018; Pringsheim et al., 2015; Soeiro-DE-Souza et al., 2015). Olanzapine/fluoxetine combination(OFC) is also a good option, which can reduce depression scores and depressive symptoms. In terms of the incidence of adverse events, OFC was the only atypical antipsychotic that did not significantly increase the incidence of adverse events. However, this does not directly indicate that OFC is more safe. Treatment-emergent weight gain and some mean and categorical fasting metabolic changes were significantly greater in OFC-treated patients (Brunner et al., 2014; Dodd & Berk, 2008). Adverse effects such as weight
gain and metabolic syndrome, somnolence, dry mouth, increased appetite and headache caused by OFC treatment should not be ignored.

Brexpiprazole is a new dopamine D2 receptor partial agonist, which is approved for the treatment of schizophrenia and for the adjunctive treatment of major depressive disorder. Brexpiprazole shares pharmacological similarities with aripiprazole. The results of network meta-analysis represented that brexpiprazole had better acceptability but no significant difference compared with placebo or other AAPs. Brexpiprazole has demonstrated a lower risk for akathisia than aripiprazole and a lower risk for somnolence than quetiapine-XR (Aftab & Gao, 2017). 3 receptor (5HT2A antagonism, 5HT1A agonism, and alpha 1B antagonism) actions are known to mitigate the akathisia and extrapyramidal side effects (EPS) associated with blocking D2 dopamine receptors (Marek & Aghajanian, 1999; Mitrano et al, 2012). H1 antagonism (i.e., antihistaminic effects) is linked to somnolence, sedation, and weight gain. Compared with aripiprazole, brexpiprazole has more potent Binding at 5HT2A, 5HT1A, and Alpha 1B receptors and Weak binding at H1 antagonism (Stahl, 2016). Therefore, the acceptability of brexpiprazole as adjuvant treatment for MDD is better.

This network meta-analysis had some limitations. First, individual studies were assessed for risk of bias; many studies did not report adequate information about randomization and allocation concealment. The final results indicated that most studies were unclear or at high risk of bias. In the GRADE framework for the primary outcomes, most comparisons were assessed as low or very low quality. Due to the overall low quality of the research, whether the estimated effect is robust and reliable and whether it can be used to guide clinical practice is limited. Second, some studies did not report changes in depression scores between baseline and end points, but instead provided scores for baseline and endpoint separately. For these studies, we calculated changes based on the baseline and endpoint scores provided, but this approach may have introduced bias in the meta-analysis. Third, the table of essential characteristics of the included literature suggests that some studies were not sponsored and were single-center studies with small sample sizes. Studies with small sample sizes are more likely to exaggerate treatment effects (Biau et al, 2008). Therefore, the results of these comparisons may be less robust and insufficient to guide clinical practice. Fourth, the RCTs included in this study had relatively short treatment durations, mainly 6 or 8 weeks, which means that the long-term efficacy and safety of adjunctive atypical antipsychotics for major depressive disorder could not be assessed. All monoamine-based antidepressant drugs are characterized by a delayed (typically more than several weeks) response to treatment (Rush et al, 2006b). Finally, this network meta-analysis set strict inclusion and exclusion criteria, excluding patients with psychiatric symptoms, psychosis, and treatment-resistant depression. It is beneficial to reduce heterogeneity and ensure transferability. However, patients with major depressive disorder had a complex condition clinically, usually associated with other psychiatric disorders, so the generalization of the results of this study was limited in the real world.

5.Conclusion

Our systematic review and network meta-analysis suggest that Adjuvant atypical antipsychotics significantly improved response rates and reduced the score of depressive rating scales compared with placebo. Aripiprazole augmentation significantly increased response rates compared with olanzapine and quetiapine. In terms of acceptability, no significant difference was found, either agents versus agents or agents versus placebo. In terms of tolerability, compared with the placebo, all AAPs were significantly less well tolerated. Adjuvant atypical antipsychotics are of great significance for improving the clinical efficacy of adult major depressive disorder. However, adverse events caused by combination therapy cannot be ignored, such as akathisia and weight gain. Clinically, the risk-benefit of adjuvant therapy with atypical antipsychotics needs to be thoroughly evaluated.

Contributors

JW and ZKQ conceived and designed the study. WWL and MTL selected the articles and extracted the data. HBW and MTL analyzed the data. JW and WWL wrote the first draft of the manuscript. JW and ZKQ interpreted the data and wrote the final version. All authors agree with the results and conclusions of
this Article.

Declaration of interest
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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