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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 (ADT). 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Methods: We searched randomized controlled trials (RCTs) published and unpublished from the date of databases and clinical trial websites inception to April 30, 2023. The evidence risk of bias (RoB) and certainty are assessed using the Cochrane bias risk tool and grading of recommendations assessment, development, and evaluation (GRADE) framework, respectively. Using network meta-analysis, we estimated summary risk ratios (RRs) or standardized mean difference (SMD) based on the random effects model.

Results: 56 eligible studies comprising 11448 participants were included. In terms of primary efficacy outcome, compared with placebo (PBO), all AAPs had significant efficacy (SMD = –0.40; 95% CI, –0.68 to –0.12 for quetiapine (QTP); –0.35, –0.59 to –0.11 for olanzapine (OLA); –0.28, –0.47 to –0.09 for aripiprazole (ARI) and –0.25, –0.42 to –0.07 for brexpiprazole (BRE), respectively). In terms of acceptability, no significant difference was found, either agents versus agents or agents versus PBO. In terms of tolerability, compared with the PBO, QTP (RR = 0.24; 95% CI,0.11–0.53), OLA (0.30,0.10–0.55), ARI (0.39,0.22–0.69), and BRE (0.37,0.18–0.75) were significantly less well tolerated. 8 (14.2%) of 56 trials were assessed as low RoB, 38 (67.9%) trials had moderate RoB, and 10 (17.9%) had high RoB; By the GRADE, the certainty of most evidence was low or very low.

Conclusion: Adjuvant AAPs had significant efficacy compared with PBO, but treatment decisions must be made to balance the risks and benefits.

Abbreviations: AAP = atypical antipsychotic, ADT = antidepressant therapy, ARI = aripiprazole, BRE = brexpiprazole, CIs = commercial industries, GRADE = grading of recommendations assessment, development, and evaluation, HAMD = Hamilton rating scale for depression, MADRS = Montgomery-Asberg depression rating scale, MDD = major depressive disorder, OFC = olanzapine/fluoxetine combination, OLA = olanzapine, PBO = placebo, QTP = quetiapine, RCTs = randomized controlled trials, RoB = risk of bias, RR = risk ratio, SMD = standardized mean difference, TRD = treatment-resistant depression.

Keywords: atypical antipsychotic, augmentation, major depressive disorder, network meta-analysis

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 yearly.[1] The prevalence of MDD is twice as high in women as in men[2] and higher in high-income countries than in low-income countries.[3] MDD is a debilitating disease characterized by depressed mood, diminished interests, impaired cognitive function, and vegetative symptoms, which is the major leading contributor

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The datasets generated during and/or analyzed during the current study are publicly available.

This study was a systematic review and network meta-analysis of atypical antipsychotics as adjunctive therapy for major depression. all analyses were based on previous published RCTs, no ethical approval or patient consent was needed.

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to chronic disease burden and disability.[4,5] Compared with the general population, patients with MDD have a higher suicide mortality rate.[6,7] The vast majority of suicides occur during a depressive episode.[8] Furthermore, some studies indicated that MDD increased the incidence rate of some primary diseases, such as hypertension, diabetes, and cognitive impairment.[9] However, a large proportion of patients with MDD did not receive proper treatment, especially in low-income countries.[10,11]

Management of MDD primarily comprises psychotherapy and pharmacological treatment.[12] Regarding pharmacological treatment, selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors are the first-line antidepressants. First-line psychological treatment recommendations for acute MDD include cognitive-behavioral therapy, interpersonal therapy, and behavioral activation (BA).[13] In addition, with further study of the pathogenesis of depression, a variety of types of compounds, including anti-inflammatory agents,[14] glutamatergic system modulators,[15] and neurokinin 1 antagonists,[16] play a 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.[17] A study[18] showed that all monoamine-based antidepressants, regardless of their pharmacological category, were only 50% effective. This inadequate response to conventional antidepressant therapy (ADT) has been termed treatment-resistant depression (TRD). Augmentation strategies refer to adding 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[19–21] recommend AAP augmentation strategies for patients with an inadequate response to ADT. To date, a total of 4 AAPs has been approved by the U.S. Food and Drug Administration for the adjunctive treatment of MDD, namely olanzapine/fluoxetine combination (OFC), aripiprazole (ARI), quetiapine (QTP) extended-release (quetiapine XR), and brexpiprazole (BRE). According to a previous meta-analysis, atypical antipsychotics (AAP) effectively augmentation antidepressants in MDD.[22] Due to the lack of head-to-head comparisons between AAP, it is impossible to assess their differences in efficacy directly. However, network meta-analysis of existing randomized controlled trials (RCTs) made it possible to compare AAPs comprehensively and understand the multiple interventions' merits and disadvantages.[23] Previous studies[24–26] utilizing NMA approaches investigated the efficacy, acceptability, and tolerability of AAPs in the treatment of TRD. However, our study differs from previous studies:

1. We included not only patients with TRD but also patients with nontreatment-resistant major depression.
2. In terms of the electronic database, besides the commonly used English database, we also included the Chinese database to increase the recall rate.
3. 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 AAP adjunctive antidepressants for treating adults with a unipolar MDD 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,[27] we did a systematic review and network meta-analysis of placebo (PBO)-controlled and head-to-head RCTs that compared an adjunctive AAP to another class of adjunctive AAP or PBO. The PRISMA checklist is shown in Supplementary Appendix 1, http://links.lww.com/MD/J636. This study is registered with PROSPERO, number CRD42022346207.

In this network meta-analysis, we searched PubMed, the Cochrane Central Register of Controlled Trials, Web of Science, Embase, PsycINFO, and China National Knowledge Infrastructure, Wan Fang database, China Science and Technology Journal Database, China Biology Medicine database for RCTs published from the date of database inception to April 30, 2023, comparing AAP with another AAP or PBO augmenting the action of antidepressants in adults (≥18 years old and 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.10th edition (ICD-10)). Meanwhile, to locate unpublished literature, we also searched Clinical Trail.gov for data supplementation with unpublished or ongoing RCTs. No language restrictions were applied. Each database takes medical subject headings and Text words to search. Take the PubMed database as an example. Details of the database searching process are shown in Supplementary Appendix 2, http://links.lww.com/MD/J637.

Exclusion criteria were: Studies including patients with bipolar depressive disorder or psychotic features. Case reports, reviews, protocols, meetings, letters, editorials, or retrospective studies were excluded. Randomized trials without a PBO or AAP.

2.2. Data extraction

Data were extracted independently by 3 investigators (W.W.L., M.T.L., H.B.W.) using data extraction forms. Disagreements will be resolved by an experienced researcher (Z.K.Q.) 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 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], nonprofit organizations, 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 (RoB) following the Cochrane Handbook for Systematic Reviews of Interventions. The bias risk for these studies was assessed based on the following 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The RoB was classified into high, unclear, or low. The included trials were graded as low, moderate, or high quality based on the following criteria[14]: trials were considered high quality when both randomization and allocation concealment were assessed as a low RoB and all other items were assessed as low or unclear RoB in a trial; a trial was judged to be of low quality when one or more of the 7 assessment domains for RoB were considered high RoB; 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.[28] Each network estimate of primary outcomes according to the criteria: RoB, indirectness, inconsistency, imprecision, and publication bias were assessed. Comparison-adjusted funnel plots were used to evaluate publication bias in the network meta-analysis.[29] We downgraded the evidence by 1 level if a domain was rated as "serious" and by 2 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 4 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 outcomes were response rate and remission rate. The response to treatment was defined as at least a 50% reduction from baseline in depression scales (MADRS or HAMD). Remission rate was defined as at least a 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 AAPs. We assessed statistical heterogeneity in each pairwise comparison using Cochrane Q test and I^2 statistics. For the Q test, a P value < .10 was considered to indicate significant heterogeneity, while for I^2, A value of I^2 = 0% to 50% was considered as low heterogeneity; 50% to 75% as moderate heterogeneity; and 75% to 90% as high heterogeneity.[30] STATA/MP (Version 16) was used to generate a network evidence plot for each outcome.[31] 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.[32] We performed effect size synthesis under the consistency model when P value > .05 and under the inconsistency model when P value < .05. The statistical inconsistency was assessed using global and local approaches to evaluate the inconsistency between direct and indirect evidence.[33] Furthermore, the node-splitting method[34] 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.[29] Finally, we performed some sensitivity analyses of the conclusions for 2 primary outcomes (primary efficacy outcome and acceptability) according to the following variables:

1. Patients with TRD (including Only studies with at least 1 inadequate response to conventional ADT).
2. High-quality study (excluding studies with a high RoB).
3. Large sample study (excluding studies with a sample size of <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), Web of Science (458), Embase (621), Cochrane Central Register of Controlled Trials (576), China National Knowledge Infrastructure database (41), Wan Fang data (212), China Biology Medicine database (41), PsycINFO (53), Clinical Trail. gov (52) and China Science and Technology Journal 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 studies (comprising 11,448 patients) met the inclusion criteria for systematic review and network analysis. The specific details of the PRISMA flow chart are shown in Figure 1.

56 studies[35–90] 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 participants had a mean age of 42.34 years (standard deviation 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 (standard deviation 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 CIs, and 34 did not declare whether to accept sponsorship; In most studies, the diagnostic criteria for MDD were DSM-IV-TR. The details of the study characteristics were presented in Table 1. The number of studies and patients with each outcome are presented in Supplementary Appendix 3, http://links.lww.com/MD/J638.

3.2. Quality assessment of included study

The studies' RoB 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 RoB 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 rater 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, and 10 (17.9%) studies were of low quality. The quality of studies included in the network meta-analysis was generally low. The RoB graph and RoB summary are reported in Supplementary Appendix 4, http://links.lww.com/MD/J639.

According to GRADE, the quality of evidence for the response and adverse events rate was rated low overall. Detailed quality of evidence assessment was shown in Supplementary Appendix 5, http://links.lww.com/MD/J640.

According to the result of the heterogeneity assessment in each comparison, in terms of primary efficacy outcome, except ARI augmentation group (I^2 = 0%), the other groups have different degrees of heterogeneity, and the specific value is (I^2 = 33% for BRE augmentation group; 74% for OFC; 92% for QTP); in terms of acceptability, BRE augmentation group (I^2 = 92%) was considered as high heterogeneity, other Groups was low heterogeneity; in terms of tolerability, all group was considered as low heterogeneity. Detailed results, including primary and secondary outcomes, were given in Supplementary Appendix 6, http://links.lww.com/MD/J641.

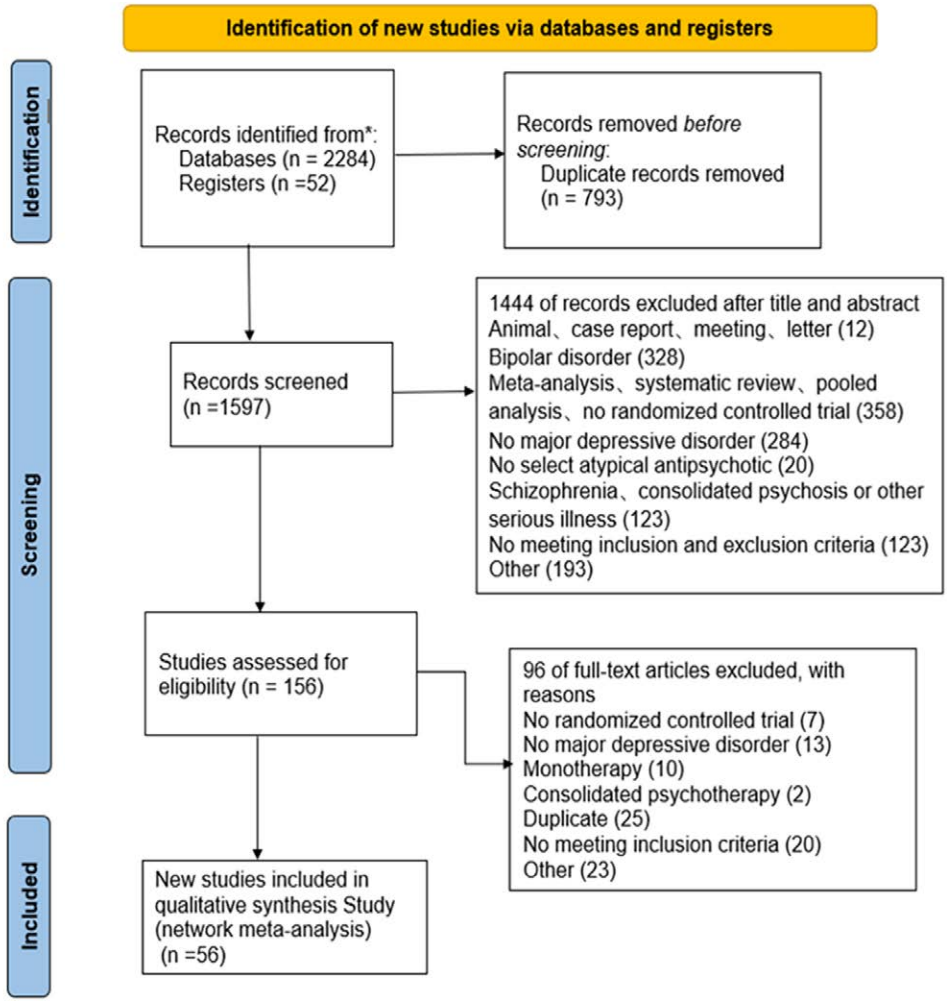

Figure 1. Flowchart of the study selection.

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 = .417), acceptability (P = .554), and tolerability (P = .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, http://links.lww.com/MD/J642).

The comparison-adjusted funnel plots of the network meta-analysis for primary outcomes did not indicate any publication bias (Supplementary Appendix 8, http://links.lww.com/MD/J643).

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, and depressive symptom score (HAMD)). All AAPs had at least 1 PBO-controlled trial. Except for the depressive symptom score (HAMD), the remaining 6 outcomes had a closed loop (BRE vs QTP vs PBO).

3.3.1. Efficacy outcomes. The results of the 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 PBO, QTP (SMD = −0.40; 95% CI, −0.68 to −0.12), olanzapine (OLA) (SMD = −0.35; 95% CI, −0.59 to −0.11), ARI (SMD = −0.28; 95% CI, −0.47 to −0.09), and BRE (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 PBO, a significant increase was found in all APPs. Compared to AAPs, ARI was associated with a higher response rate than OLA (RR 1.22, 95% CI 1.07–1.40), QTP (RR 0.76,95% CI 0.66–0.88) were less efficacious than ARI.

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 7524 patients) were included in the acceptability analysis; no significant difference was found in 4 AAPs than PBO. In terms of tolerability, a total of 20 studies (comprising 6524 patients) were included in the tolerability analysis. Compared with the PBO, QTP (RR = 0.24; 95% CI,0.11–0.53), OLA (RR = 0.30; 95% CI, 0.10–0.55), ARI (RR = 0.39; 95% CI,0.22–0.69), and BRE (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, http://links.lww.com/MD/J644.

Table 1

Characteristics of included studies.

	Study name	Mean age (SD)	Female n (%)	No. randomised	Drug (dose of synergist(min-max,mg, daily))	Duration (wk)	Baseline severity scale	Baseline severity, mean (SD)	Multi/single centre	Sponsored	Outcome measurement
1	Thase, M. E 2015a	46.6 (11.0)	146 (66.1)	221	Placebo + ADT	6	MADRS	26.3 (5.3)	Multi	Cls	①②③④⑤⑥⑦
		45.7 (11.6)	158 (69.9)	226	brexpiprazole 1 mg + ADT			26.7 (5.6)			
		44.5 (11.2)	158 (69.9)	230	brexpiprazole 3 mg + ADT			26.4 (5.2)			
2	Thase, M. E 2015b	44.1 (11.6)	130 (69.1)	188	ADT + brexpiprazole	6	MADRS	26.6 (5.8)	Multi	Cls	①②③④⑤⑥⑦
		45.2 (11.3)	137 (71.7)	191	ADT + placebo			27.1 (5.6)			
3	Hobart, M 2018a	41.8 (11.7)	149 (72.3)	206	ADT + placebo	6	MADRS	25.4 (5.2)	Multi	Cls	①②③⑤⑥
		43.6 (11.5)	128 (65.0)	197	ADT + brexpiprazole 2–3mg			25.4 (5.1)			
		44.6 (11.6)	66 (66.0)	100	ADT + quetiapine XR 150–300mg			25.6 (5.5)			
4	Hobart, M.2018 b	42.7 (12.5)	144 (71.3)	202	ADT + Placebo	6	MADRS	26.2 (6.2)	Multi	Cls	①②③⑤⑥
		43.0 (12.7)	147 (76.6)	192	ADT + brexpiprazole 2mg			27.1 (5.7)			
5	NCT01838681	47.1 (12.1)	307 (69.1)	444	ADT + brexpiprazole 1–3mg	6	MADRS	25.9 (4.1)	Multi	Cls	①
		46.4 (12.1)	302 (68.5)	441	ADT + Placebo			25.8 (4.1)			
6	NCT01052077	44.7 (11.7)	123 (66.5)	185	ADT + brexpiprazole 1–3mg	6	NA	NA	Multi	Cls	①②③④⑤⑥⑦
		42.4 (11.7)	130 (69.5)	187	ADT + placebo			NA			
7	NCT00797966	43.9 (10.8)	41 (66.1)	62	ADT + brexpiprazole 0.15	6	MADRS	NA	Multi	Cls	①②③⑦
		44.0 (11.8)	86 (71.7)	120	ADT + brexpiprazole 0.25–0.75mg			NA			
		43.7 (11.6)	80 (66.1)	121	ADT + brexpiprazole 1–2mg			NA			
		43.3 (11.5)	82 (65.1)	126	ADT + Placebo			NA			
8	Shelton 2005	42.5 (10.7)	98 (67.1)	146	Olanzapine 6–12mg + FLX	8	MADRS	28.5 (7.5)	Multi	Cls	①④⑤⑥
		41.7 (11.0)	103 (72.5)	142	FLX + Placebo			28.4 (7.3)			
9	Thase 2007	43.3 (10.8)	63 (61.8)	200	Olanzapine 6–18mg + FLX	8	MADRS	29.5 (7.1)	Multi	Cls	①④⑤⑦
		44.8 (10.0)	63 (61.8)	206	FLX + Placebo			29.7 (6.9)			
	Thase 2007	45.3 (9.5)	69 (70.4)	200	Olanzapine 6–18mg + FLX	8	MADRS	30.6 (6.1)	Multi	Cls	①④⑤⑦
		44.5 (9.9)	67 (65.7)	206	FLX + Placebo			30.1 (5.9)			
10	Cui YN 2017	37.5 (3.1)	7 (41.1)	17	Olanzapine 2.5–5mg + FLX	8	HAMD	NA	Single	Unclear	②⑥
		39.2 (3.3)	6 (35.2)	17	FLX + Placebo			NA			
11	Ding SY 2017	47.4 (3.9)	13 (40.6)	32	Olanzapine 2.5–5mg + FLX	8	HAMD-17	26.1 (3.7)	Single	Unclear	⑥⑦
		46.9 (3.7)	12 (37.5)	32	FLX + Placebo			26.7 (3.9)			
12	Dong KY 2016	49.5 (2.6)	46 (51.1)	90	Olanzapine 2.5–5mg + FLX	8	HAMD	NA	Single	Unclear	②⑥
		46.5 (1.3)	47 (52.2)	90	FLX + Placebo			NA			
13	Du W 2017	NA	NA	45	Olanzapine 5mg + FLX	8	HAMD	36.5 (4.7)	Single	Unclear	⑦
		NA	NA	45	FLX + Placebo			37.1 (4.8)			
14	Duan W 2021	65 (8)	11 (27.5)	40	Olanzapine 2.5–15mg + FLX	8	HAMD	36.85 (4.44)	Single	Unclear	②⑥⑦
		65.5 (9.5)	12 (30)	40	FLX + Placebo			36.84 (4.53)			
15	Fu J 2018	41.25 (5.18)	26 (40.6)	64	Olanzapine 2.5–5mg + FLX	8	HAMD	NA	Single	Unclear	②⑥
		40.56 (6.04)	27 (42.1)	64	FLX + Placebo			NA			
16	Guo L 2015	49.5 (2.6)	46 (51.1)	90	Olanzapine 2.5–5mg + FLX	8	HAMD	NA	Single	Unclear	②⑥
		46.5 (1.3)	47 (52.2)	90	FLX + Placebo			NA			
17	Hu HT 2016	NA	NA	47	Olanzapine 2.5–5mg + FLX	8	HAMD	NA	Single	Unclear	②⑥
		NA	NA	47	FLX + Placebo			NA			
18	Huang XJ 2021	38.79 (5.37)	24 (58.5)	41	Olanzapine 2.5–5mg + FLX	8	HAMD	NA	Single	Unclear	⑥⑦
		38.83 (5.42)	23 (56.1)	41	FLX + Placebo			NA			

(*Continued*)

Table 1

(Continued)

	Study name	Mean age (SD)	Female n (%)	No. randomised	Drug (dose of synergist(min-max,mg, daily))	Duration (wk)	Baseline severity scale	Baseline severity, mean (SD)	Multi/single centre	Sponsored	Outcome measurement
19	Jia QM 2015	36.3 (9.2)	22 (44)	50	Olanzapine 2.5–5mg + FLX	8	HAMD	NA	Single	Unclear	②
		36.9 (9.7)	23 (46)	50	FLX + Placebo			NA			
20	Li YY 2017	37.13 (1.6)	20 (46.5)	43	Olanzapine 2.5–5mg + FLX	8	HAMD	NA	Single	Unclear	②⑥⑦
		37.15 (1.62)	21 (48.8)	43	FLX + Placebo			NA			
21	Li Y 2017	41.7 (5.3)	21 (43.75)	48	Olanzapine 2.5–5mg + FLX	8	HAMD	25.9 (1.7)	Single	Unclear	②⑥
		42.1 (5.2)	20 (41.7)	48	FLX + Placebo			26.1 (1.9)			
22	Liang LJ 2014	36. 8 (2. 6)	23 (43.3)	53	Olanzapine 2.5–5mg + FLX	8	HAMD	NA	Single	Unclear	②
		35. 8 (2. 8)	20 (37.7)	53	FLX + Placebo			NA			
23	Liu YP 2012	NA	NA	50	Olanzapine 2.5–5mg + FLX	8	HAMD-17	NA	Single	Unclear	②③⑥
		NA	NA	50	FLX + Placebo			NA			
24	Pu MX 2017	42.26 (4.42)	32 (47.0)	68	Olanzapine 2.5–5mg + FLX	8	HAMD-17	28.84 (3.29)	Single	Unclear	②⑥
		42.28 (4.46)	31 (45.5)	68	FLX + Placebo			28.82 (3.36)			
25	Shi Y 2020	NA	10 (45.4)	22	Olanzapine 2.5mg + FLX	8	HAMD	36.99 (3.65)	Single	Unclear	⑥
		NA	11 (50)	22	FLX + Placebo			37.44 (4.28)			
26	Song Y 2018	48.6 (9.4)	19 (47.5)	40	Olanzapine 2.5–5mg + FLX	8	HAMD	NA	Single	Unclear	②⑥
		47.2 (8.9)	18 (45)	40	FLX + Placebo			NA			
27	Tu XS 2016	38.5 (10.0)	18 (45)	40	Olanzapine 2.5–5mg + FLX	8	HAMD	26.5 (2.1)	Single	Unclear	②⑥
		39.5 (10.0)	20 (50)	40	FLX + Placebo			25.5 (2.3)			
28	Wang J 2017	NA	19 (44.19)	43	Olanzapine 2.5–5mg + FLX	8	HAMD	NA	Single	Unclear	②
		NA	20 (46.51)	43	FLX + Placebo			NA			
29	Berman 2009	45.1 (10.6)	138 (78.0)	177	Aripiprazole2–20mg + ADT	6	MADRS	26.6 (5.8)	Multi	Cls	①②③④⑤⑥
		45.6 (11.3)	117 (68.0)	172	placebo + ADT			27.1 (5.8)			
30	Berman 2007	46.5 (10.6)	112 (61.5)	182	Aripiprazole2–20mg + ADT	6	MADRS	26.0 (6.1)	Multi	Cls	①②③④⑤⑥
		44.2 (10.9)	113 (64.2)	176	placebo + ADT			25.9 (6.5)			
31	Kamijima 2013	39.2 (9.1)	73 (37.1)	197	Aripiprazole 3mg + ADT	6	MADRS	25.2 (7.2)	Multi	Cls	①②④⑤⑥
		38.1 (9.6)	93 (47.9)	194	Aripiprazole 3–15mg + ADT			25.3 (7.3)			
		38.7 (9.2)	80 (41.0)	195	placebo + ADT			25.5 (7.4)			
32	Kamijima 2018	38.3 (11.8)	79 (38.0)	208	Aripiprazole 3–12mg + ADT	6	MADRS	24.9 (6.6)	Multi	Cls	①②③④⑤⑥⑦
		39.5 (11.8)	72 (35.5)	203	placebo + ADT			25.2 (6.5)			
33	Marcus 2008	44.6 (11.0)	126 (66.0)	191	Aripiprazole 2–20mg + ADT	6	MADRS	25.2 (6.2)	Multi	Cls	①②③④⑤
		44.4 (10.7)	128 (67.4)	190	placebo + ADT			27.0 (5.5)			
34	Li XX 2020	41.29 (6.48)	26 (43.3)	60	Aripiprazole 5–10mg + ADT	8	HAMD-17	36.44 (2.97)	Single	Unclear	⑦
		43.15 (7.15)	32 (53.3)	60	placebo + ADT			37.56 (3.01)			
35	Liang XL 2020	40.5 (9.9)	16 (51.6)	31	Aripiprazole 10–15mg + ADT	6	HAMD	27.9 (4.1)	Single	Unclear	②⑥⑦
		39.7 (8.7)	11 (35.4)	31	placebo + ADT			28.2 (3.7)			
36	Wang KP 2020	38.62 (5.75)	14 (43.7)	32	Aripiprazole10–20mg + ADT	8	HAMD-17	26.49 (1.31)	Single	Unclear	②
		39.35 (6.24)	15 (46.8)	32	placebo + ADT			27.13 (1.42)			
37	Zhang J 2012	33.3 (9.8)	16 (57.1)	28	Aripiprazole 5–15mg + ADT	8	HAMD	29.3 (3.3)	Single	Unclear	②⑥⑦
		31.6 (9.3)	18 (64.3)	28	placebo + ADT			28.4 (3.7)			
38	NCT01111552	NA	NA	23	Aripiprazole 3–12mg + ADT	6	MADRS	NA	Multi	Cls	①⑥
		NA	NA	22	placebo + ADT			NA			
39	NCT01111565	NA	NA	16	Aripiprazole 3–12mg + ADT	6	HAMD-17	NA	Multi	Cls	①④⑤⑥
		NA	NA	14	placebo + ADT			NA			
40	NCT01111539	NA	NA	28	Aripiprazole 6–12mg + ADT	6	HAMD-17	NA	Multi	Cls	①④⑤⑥
		NA	NA	28	placebo + ADT			NA			
41	Bauer 2009	44.8 (10.4)	104 (65.0)	160	Placebo + ADT	6	NA	28.2 (5.6)	Multi	Cls	①②③⑤⑥⑦
		46.0 (10.1)	115 (69.3)	166	Quetiapine XR 150mg			28.6 (5.4)			
		45.5 (11.1)	110 (68.3)	161	Quetiapine XR 300mg			28.4 (5.5)			

(*Continued*)

Table 1

(Continued)

	Study name	Mean age (SD)	Female n (%)	No. randomised	Drug (dose of synergist(min-max,mg, daily))	Duration (wk)	Baseline severity scale	Baseline severity, mean (SD)	Multi/single centre	Sponsored	Outcome measurement
42	El-Khalili 2010	46.2 (10.9)	98 (68.5)	143	Placebo + ADT	6	MADRS	27.6 (5.5)	Multi	Cls	①②③⑤⑥⑦
		45.9 (11.0	109 (76.2)	143	Quetiapine XR 150mg + ADT			27.2 (5.2)			
		44.3 (11.3)	106 (72.6)	146	Quetiapine XR 300mg + ADT			27.6 (5.0)			
43	McIntyre 2007	44 (10)	18 (65)	29	Quetiapine XR 50–600mg + ADT	8	HAM-D17	23.4 (3.0)	Single	Unclear	②③⑥
		45 (12)	17 (59)	29	Placebo + ADT			23.2 (2.2)			
44	Moica 2018	40.27	26 (72.2)	36	Quetiapine XR 50–150mg + ADT	8	HAM-D17	22.17 (3.23)	Single	Unclear	⑦
		39.25	28 (77.7)	36	Placebo + ADT			24.61 (4.19)			
45	Duan CF 2012	32.5 (5.7)	18 (60.0)	30	Quetiapine XR 50–300mg + ADT	6	HAMD	NA	Single	Unclear	②⑥
		32.8 (5.6)	19 (63.3)	30	placebo + ADT			NA			
46	Duan J 2017	39.1 (6.7)	22 (33.8)	65	Quetiapine XR 50–750mg + ADT	8	HAMD	51.2 (12.3)	Single	Unclear	②⑥
		38.2 (6.6)	29 (44.6)	65	placebo + ADT			50.9 (11.6)			
47	Gao DQ 2020	44.64 (18.32)	31 (62.0)	50	Quetiapine XR 50–150mg + ADT	8	HAMD	28.62 (2.66)	Single	Unclear	②⑥⑦
		45.58 (16.77)	29 (58.0)	50	Placebo + ADT			29.08 (2.83)			
48	Liu L 2006	31.3 (6.5)	16 (48.4)	33	Quetiapine XR 100–400mg + ADT	6	HAMD	28.4 (5.3)	Single	Unclear	②⑥⑦
		30.2 (6.3)	14 (51.8)	27	placebo + ADT			29.6 (4.9)			
49	Peng BQ 2017	45.74 (3.85)	19 (44.1)	43	Quetiapine XR 100–400mg + ADT	8	HAMD	NA	Single	Unclear	②⑥
		45.25 (3.58)	20 (46.5)	43	placebo + ADT			NA			
50	Shi QS 2021	44.27 (3.72)	21 (61.7)	34	Quetiapine XR 50–150mg + ADT	8	MADRS	33.02 (2.41)	Single	Unclear	①⑥⑦
		44.31 (3.74)	20 (58.8)	34	placebo + ADT			32.97 (2.38)			
51	Zhang CL 2015	32.01 (11.98)	24 (45.1)	52	Quetiapine XR 100–300mg + ADT	8	HAMD-24	57.41 (13.74)	Single	Unclear	②⑥⑦
		33.56 (13.10)	29 (55.7)	52	placebo + ADT			52.57 (17.48)			
52	Zhang HT 2014	32.6 (7.3)	17 (42.5)	40	Quetiapine XR 50–250mg + ADT	8	HAMD	33.78 (5.63)	Single	Unclear	⑥⑦
		32.8 (7.6)	16 (40.0)	40	placebo + ADT			34.23 (6.23)			
53	Zhou P 2019	39.01 (6.8)	13 (43.3)	30	Quetiapine XR 50–600mg + ADT	8	HAMD	51.3 (11.7)	Single	Unclear	⑥⑦
		38.25 (6.7)	12 (40)	30	placebo + ADT			51.1 (11.8)			
54	Shelton 2001	NA	NA	10	Olanzapine 5–20mg + FLX	8	MADRS	NA	Single	Cls	①②④⑤⑦
		NA	NA	10	FLX + Placebo			NA			
55	Corya 2006	NA	NA	243	Olanzapine 7.9mg + FLX	12	MADRS	NA	Multi	Cls	①②③④⑤
		NA	NA	60	FLX + Placebo			NA			
56	Fava 2012	45.36 (10.35)	37 (66.07)	56	Aripiprazole 2 mg + ADT	4	MADRS	NA	Multi	Cls	①②④⑤
		45.06 (11.34)	108 (63.91)	169	placebo + ADT			NA			

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

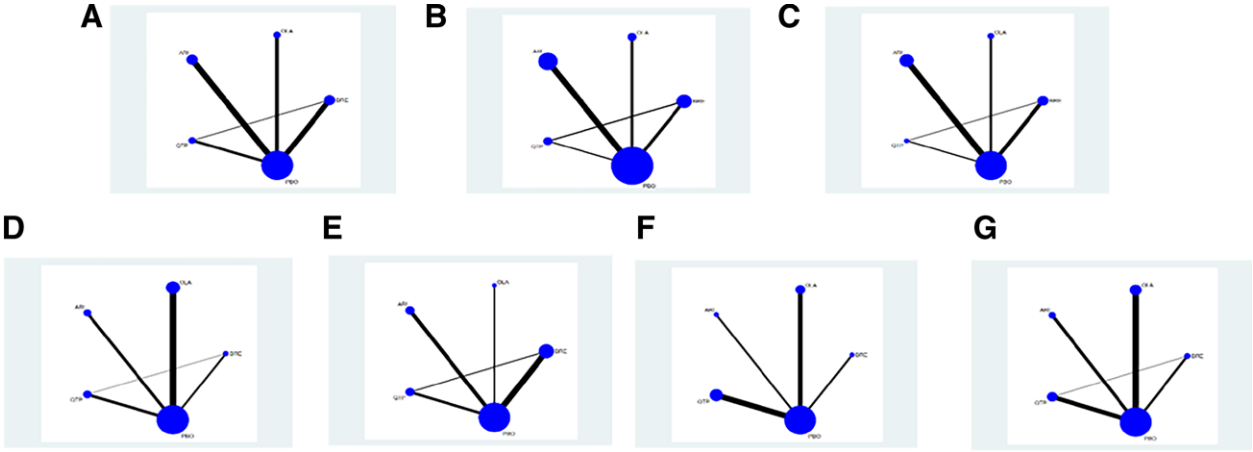

Figure 2. Network of eligible comparisons for 7 outcomes. (A) (depressive symptom score (MADRS)); (B) (acceptability); (C) (tolerability); (D) (response rate); (E) (remission rate); (F) (depressive symptom score (HAMD)); (G) (adverse events incidence rate). The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants (sample size).

Depression symptom scores(SMD[95%,CI]) Comparison Response rate(RR[95%,CI])

BRE	0.92 (0.77,1.08)	1.12 (0.92,1.37)	0.85 (0.72,1.01)	***0.72 (0.61,0.84)***
0.11 (-0.19,0.40)	OLA	***1.22 (1.07,1.40)***	0.93 (0.85,1.02)	***0.79 (0.74,0.83)***
0.04 (-0.22,0.30)	-0.07 (-0.38,0.24)	ARI	***0.76 (0.66,0.88)***	***0.64 (0.57,0.73)***
0.15 (-0.15,0.46)	0.05 (-0.31,0.40)	0.12 (-0.23,0.46)	QTP	***0.85 (0.79,0.91)***
-0.25 (-0.42,-0.07)	***-0.35 (-0.59,-0.11)***	***-0.28 (-0.47,-0.09)***	***-0.40 (-0.68,-0.12)***	PBO

Figure 3. Network meta-analysis of depression symptom score (MADRS) and response rate. To obtain RRs for comparisons in the opposite direction, reciprocals should be taken. The significant results were bolded and tilted. ARI = aripiprazole, BRE = brexpiprazole, CI = confidence interval, OLA = olanzapine, QTP = quetiapine, PBO = placebo, RR = risk ratio, SMD = standardized mean difference.

All-cause discontinuation(RR[95%,CI]) Comparison Side-effect discontinuation(RR[95%,CI])

BRE	1.22 (0.48,3.14)	0.94 (0.37,2.37)	1.52 (0.57,4.05)	***0.37 (0.18,0.75)***
0.83 (0.39,1.79)	OLA	0.77 (0.33,1.78)	1.24 (0.46,3.38)	***0.30 (0.16,0.55)***
0.83 (0.44,1.58)	1.00 (0.49,2.05)	ARI	1.61 (0.60,4.31)	***0.39 (0.22,0.69)***
0.82 (0.42,1.59)	0.99 (0.41,2.39)	0.99 (0.45,2.15)	QTP	***0.24 (0.11,0.53)***
0.92 (0.56,1.51)	1.10 (0.61,1.99)	1.10 (0.73,1.67)	*1.12 (0.58,2.16)*	PBO

Figure 4. Network meta-analysis of acceptability and tolerability. To obtain RRs for comparisons in the opposite direction, reciprocals should be taken. The significant results were bolded and tilted. ARI = aripiprazole, BRE = brexpiprazole, CI = confidence interval, OLA = olanzapine, PBO = placebo, QTP = quetiapine, RR = risk ratio.

Based on cumulative probability plots and surface under the cumulative ranking curves, Table 2 and Figure 5 show the ranking of medications of 7 outcomes. The ranking for MDD patients of primary efficacy outcome from high to low was as follows: QTP, OLA, ARI, BRE, and PBO. In terms of acceptability, each treatment group was ranked BRE, PBO, OLA, ARI, and QTP from largest to smallest. In terms of tolerability, each treatment group was ranked PBO, ARI, BRE, OLA, and QTP from largest to smallest. In addition, in terms of response rate and remission rate, ARI ranked first.

3.4. Sensitivity analysis of the primary outcome

Sensitivity analyses of the primary efficacy and acceptability outcomes were performed in 3 domains patients with TRD (including only studies with at least 1 inadequate response to conventional ADT); High-quality study (excluding studies with a high RoB); Large sample study (excluding studies with a sample size of <30). The results of the 3 sensitivity analysis were robust. The sensitivity analyses results for primary efficacy and acceptability outcomes were presented in Supplementary Appendix 10, http://links.lww.com/MD/J645.

4. Discussion

Based on 56 studies comprising 57 RCTs, this network meta-analysis examined the efficacy and safety of AAPs as adjunctive treatment in patients with a unipolar MDD. 4 AAPs (OFC, ARI, QTP, and BRE) approved by the U.S. FDA for adjunctive treatment of MDD were included.

Table 2

SUCRA Probability ranking of outcome indicators.

Comparision	The mean change in MADRS total score from baseline to endpoint		All-cause discontinuation		side-effects Discontinuation		Remission rate		Adverse events incidence rate		Response rate		The mean change in HAMD total score from baseline to endpoint	
	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank
BRE + ADT	45.1	4	68.1	1	47.6	3	48.5	3	22.6	4	73.6	2	22.1	4
OLA + ADT	70.5	2	42.6	3	31.6	4	74.6	2	98.4	1	52.4	3	97.1	1
ARI + ADT	54.6	3	41.0	4	52.9	2	81.0	1	9.6	5	96.6	1	73.5	2
QTP + ADT	79.6	1	40.5	5	18.0	5	45.3	4	43.9	3	27.3	4	50.3	3
PBO + ADT	0.2	5	57.8	2	99.9	1	0.5	5	75.5	2	0.0	5	7.0	5

ADT = antidepressant therapy, ARI = aripiprazole, BRE = brexpiprazole, OLA = olanzapine, PBO = placebo, QTP = quetiapine, SUCRA = surface under the cumulative ranking curve.

In terms of primary efficacy outcome, all AAPs showed significant efficacy compared with PBO, but no significant differences were found among AAPs. In terms of acceptability, no significant difference was found between AAPs and PBO. 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 PBO, all AAPs significantly increased response rate. In addition, ARI was superior to QTP and OLA among AAPs. In terms of incidence of adverse events, except for OLA, the incidence of other AAPs adverse events was significantly higher than that with PBO.

In summary, all AAPs were superior to PBO in reducing depression scores and improving response rates, which is consistent with previous studies.[24,26] This study further validates the effectiveness of adjunctive AAPs 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 quality assessment, most studies were unclear or at high RoB. Many of the Chinese RCTs included in this study were rated as a moderate risk due to a lack of detailed description of randomization, allocation, and blinding. According to GRADE, the quality of evidence for primary outcomes was rated as very low or low overall. The sensitivity analysis results (including only studies with a diagnosis of TRD, excluding studies with small sample size, and excluding studies with high risk) were robust.

ARI ranked first in improving response and remission rates and second in reducing depression scores (HAMD scales) from baseline to endpoint. ARI is the first AAP drug approved by the U.S. FDA for the adjunctive treatment of MDD. Furthermore, ARI is a primary recommendation for inadequate response to ADT.[19] Adjunctive ARI has significant clinical benefits compared with PBO. In terms of tolerability, ARI augmentation did not produce more discontinuations due to adverse events than PBO. Compared with other AAPs, ARI was better but not significantly different. Overall, ARI had higher efficacy and better tolerability among AAPs. ARI pharmacology—is characterized by its unique agonist activity at dopamine D_2, D_3 and serotonin 5-HT_{1A} receptors, as well as antagonist activity at serotonin 5-HT_{2A} receptors.[91] Unfortunately, ARI augmentation had significantly higher rates of adverse events than PBO. The most common adverse events with ARI[22,92,93] included akathisia, fatigue, and weight gain, which may account for the higher rate of adverse events in the ARI augmentation group.

QTP 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 QTP has been demonstrated in patients with TRD, either as monotherapy or as augmentation therapy.[94–97] 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 AAP that did not significantly increase the incidence of adverse events. However, this does not directly indicate that OFC is safer. Treatment-emergent weight gain and some mean and categorical fasting metabolic changes were significantly greater in OFC-treated patients.[98,99] Adverse effects such as weight gain and metabolic syndrome, somnolence, dry mouth, increased appetite, and headache caused by OFC treatment should not be ignored.

BRE is a new dopamine D_2 receptor partial agonist, which is approved for the treatment of schizophrenia and for the adjunctive treatment of MDD. BRE shares pharmacological similarities with ARI. The network meta-analysis represented that BRE had better acceptability but no significant difference compared with PBO or other AAPs. BRE has demonstrated a lower risk for akathisia than ARI and a lower risk for somnolence than QTP-XR.[100] 3 receptor (5HT2A antagonism, 5HT1A agonism, and alpha 1B antagonism) actions are known

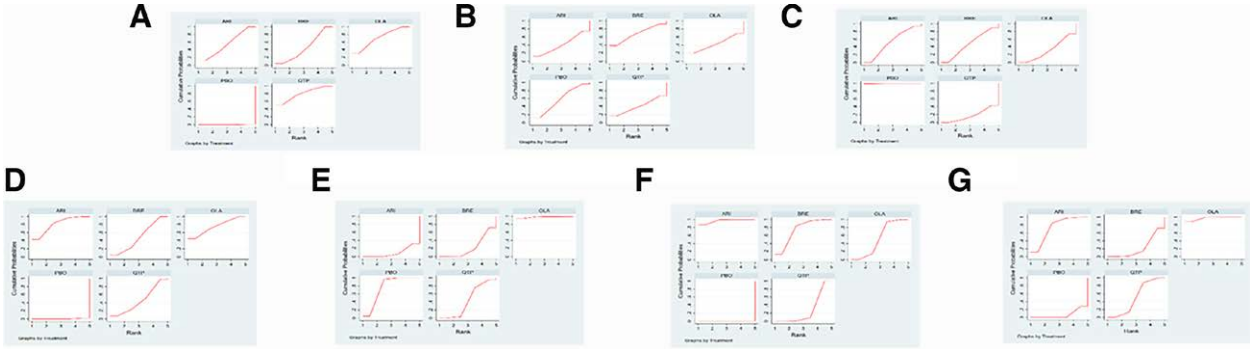

Figure 5. The ranking of TCMIs based on cumulative probability plots and SUCRA. (A) (depressive symptom score (MADRS)), (B) (acceptability), (C) (tolerability), (D) (remission rate), (E) (adverse events incidence rate), (F) (response rate), (G) (depressive symptom score (HAMD)). SUCRA = surface under the cumulative ranking curve.

to mitigate the akathisia and extrapyramidal side effects (EPS) associated with blocking D2 dopamine receptors.[101,102] H1 antagonism (i.e., antihistaminic effects) is linked to somnolence, sedation, and weight gain. Compared with ARI, BRE Has more potent Binding at 5HT2A, 5HT1A, and Alpha 1B receptors and Weak binding at H1 antagonism.[103] Therefore, the acceptability of BRE as an adjuvant treatment for MDD is better.

This network meta-analysis had some limitations. First, individual studies were assessed for RoB; many studies did not report adequate information about randomization and allocation concealment. The final results indicated that most studies were unclear or at high RoB. Most comparisons were assessed as low or very low quality in the GRADE framework for the primary outcomes. 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 endpoints but instead provided scores for baseline and endpoints separately. 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.[104] 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 AAPs for MDD could not be assessed. All monoamine-based antidepressant drugs are characterized by a delayed (typically more than several weeks) response to treatment.[105] Finally, this network meta-analysis set strict inclusion and exclusion criteria, excluding patients with psychiatric symptoms or psychosis. It is beneficial to reduce heterogeneity and ensure transferability. However, patients with MDD 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 AAPs significantly improved response rates and reduced the score of depressive rating scales compared with PBO. ARI augmentation significantly increased response rates compared with OLA and QTP. In terms of acceptability, no significant difference was found, either agents versus agents or agents versus PBO. In terms of tolerability, compared with the PBO, all AAPs were significantly less well tolerated. Adjuvant AAPs are of great significance for improving the clinical efficacy of adult MDD. However, adverse events caused by combination therapy cannot be ignored, such as akathisia and weight gain. Clinically, the risk-benefit of adjuvant therapy with AAPs needs to be thoroughly evaluated.

Author contributions

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