

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Methods: We searched randomized controlled trials (RCTs) published and unpublished from the date of databases and clinical trial websites inception to April 30, 2023.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 \leq 7 (MADRS \leq 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 I², 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.

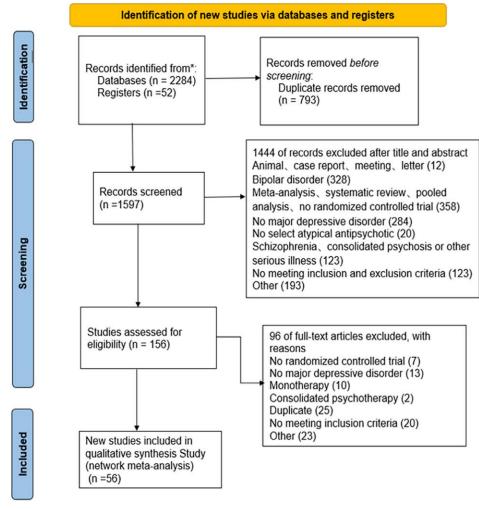


Figure 1. Flowchart of the study selection.

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.

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NULLINGSOOT 44.1 (12) 3.0.1 (13) 3.0.1 (NC1010350501 44.1 AUT + herophane 1-3rg b MAUN 25.9 (4.1) Mult CS CO NC101052077 44.7 (11.7) 132 (65.3) 135 AUT + herophazele 1.57 b MAUN 25.9 (4.1) Mult CS CO CO VC10052075 44.7 (11.7) 132 (65.3) 135 AUT + herophazele 0.15 C MUL MUR CS CO CO <t< td=""><td>ι</td><td></td><td>43.0 (12.7)</td><td>147 (76.6)</td><td>192</td><td>ADT + brexpiprazole 2mg</td><td>c</td><td></td><td>27.1 (5.7)</td><td></td><td>ō</td><td>(</td></t<>	ι		43.0 (12.7)	147 (76.6)	192	ADT + brexpiprazole 2mg	c		27.1 (5.7)		ō	(
WCT01050/T 47.11/1 723 (66.3) 167 AUT + hreepinate 1-3mg 6 NA NA Main C/S ACT0105207 42.3 (11.7) 723 (66.3) 167 AUT + hreepinate 1-3mg 6 NA NA Main C/S ACT0105207 42.3 (11.7) 323 (66.3) 167 AUT + hreepinate 0.25-0.75mg 6 MABS NA Main C/S AS3 (11.5) 82 (61.1) 120 AUT + hreepinate 0.25-0.75mg 6 MABS NA Main C/S AS3 (11.5) 82 (61.1) 133 (7.2) 121 AUT + hreepinate 0.25-0.75mg NA NA Main C/S Thase 2007 433 (10.3) 83 (1.3) 200 Diarzapite C-18mg + LX 8 MADRS 22.6 (7.1) Main C/S Thase 2007 433 (10.3) 63 (1.3) 14.1 Diarzapite C-18mg + LX 8 MADRS 22.6 (7.1) Main C/S Thase 2007 433 (3.3) 23 (3.3) 23 (3.3) 23 (3.1) 23 (3.1) 23 (3.1) <td>WCT0105077 4477117 775 (65.0) 185 Mit + hendbox (11.1) Cit Mit Cit Cit</td> <td>Ω</td> <td>NCI 01838681</td> <td>47.1 (12.1) 46.4 (12.1)</td> <td>307 (69.1) 302 (68.5)</td> <td>444 441</td> <td>ADI + Drexpiprazole 1–3mg ADT + Placeho</td> <td>Q</td> <td>MADHS</td> <td>25.9 (4.1) 25.8 (4.1)</td> <td>Multi</td> <td>CIS</td> <td>Ð</td>	WCT0105077 4477117 775 (65.0) 185 Mit + hendbox (11.1) Cit Mit Cit	Ω	NCI 01838681	47.1 (12.1) 46.4 (12.1)	307 (69.1) 302 (68.5)	444 441	ADI + Drexpiprazole 1–3mg ADT + Placeho	Q	MADHS	25.9 (4.1) 25.8 (4.1)	Multi	CIS	Ð
NCTO0737965 22.4 (11.7) 130 (55.1) 137 ADT + phenologicale 0.15 N	NCTOOP37966 42.4 (17) 130 (66.1) 127 ADTT + pleetion NM MM MM CS CS <td>9</td> <td>NCT01052077</td> <td>44.7 (11.7)</td> <td>123 (66.5)</td> <td>185</td> <td>ADT + brexpiprazole 1–3mg</td> <td>9</td> <td>NA</td> <td>NA</td> <td>Multi</td> <td>CIS</td> <td>(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,</td>	9	NCT01052077	44.7 (11.7)	123 (66.5)	185	ADT + brexpiprazole 1–3mg	9	NA	NA	Multi	CIS	(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
WCT00737966 64 (0) (1) (1) (1) (1) (1) (1) (1) (1) (1) (1	WCT00757966 430 (10) 66 (71) 100 ADT + herepiperable 0.15, M Multi CIs O.G 437 (11) 66 (71) 101 MOT + herepiperable 1-25-07,5mg M<			42.4 (11.7)	130 (69.5)	187	ADT + placebo			NA			
437 (11) 86 (7.1) 120 ADT + breexplorated (25-0.75mg) NM 437 (11) 80 (67.1) 121 ADT + breexplorated (1-2mg) NM 437 (11) 80 (67.1) 121 ADT + breexplorated (1-2mg) NM These 2007 423 (10.1) 80 (67.1) 122 ADT + precebo ADT + precepo These 2007 423 (10.0) 63 (1.0) 133 (7.2) 146 Other approxeme (-1m + FX 8 MADRS 235 (7.2) MU Cs 9 These 2007 433 (10.0) 63 (1.0) 133 (7.2) 147 Darraphee (-1m + FX 8 MADRS 235 (7.1) MU Cs These 2007 453 (9.0) 63 (1.0) 200 Darraphee (-1m + FX 8 MADRS 235 (7.1) MU Cs Ding SY 2017 453 (9.0) 63 (1.0) 200 Darraphee (-1m + FX 8 HAMD NA Single Uncear Ding SY 2017 453 (9.0) 7 (41.1) 17 Darraphee (-1m + FX 8 HAMD NA Single <td>ATT (11) B(71) T20 ATT Herophazabe 1-2mg M 437 (115) 86 (71) 120 ATT Herophazabe 1-2mg M M 437 (115) 86 (71) 126 ATT Herophazabe 1-2mg M M 112 110 103 (725) 126 ATT Herophazabe 1-2mg M 17 hase 2007 43.3 (115) 87 (51) 126 Ohrespine 6-18mg + RX 8 MADRS 225 (71) Mult Cls 0 17 hase 2007 43.3 (10) 53 (51) 200 Ohrespine 6-18mg + RX 8 MADRS 223 (73) Mult Cls 0 17 hase 2007 453 (10) 53 (51) 7 (41) 17 Ohrespine 6-18mg + RX 8 MADRS 236 (71) Mult Cls 0 0 10m SY 2017 473 (30) 51 (53) 7 (41) 17 Ohrespine 5-5mg + LX 8 HAMD17 267 (33) Mult Cls 0 0 0 0 0 0 0 0 0 0</td> <td>7</td> <td>NCT00797966</td> <td>43.9 (10.8)</td> <td>41 (66.1)</td> <td>62</td> <td>ADT + brexpiprazole 0.15</td> <td>9</td> <td>MADRS</td> <td>NA</td> <td>Multi</td> <td>CIS</td> <td>0230</td>	ATT (11) B(71) T20 ATT Herophazabe 1-2mg M 437 (115) 86 (71) 120 ATT Herophazabe 1-2mg M M 437 (115) 86 (71) 126 ATT Herophazabe 1-2mg M M 112 110 103 (725) 126 ATT Herophazabe 1-2mg M 17 hase 2007 43.3 (115) 87 (51) 126 Ohrespine 6-18mg + RX 8 MADRS 225 (71) Mult Cls 0 17 hase 2007 43.3 (10) 53 (51) 200 Ohrespine 6-18mg + RX 8 MADRS 223 (73) Mult Cls 0 17 hase 2007 453 (10) 53 (51) 7 (41) 17 Ohrespine 6-18mg + RX 8 MADRS 236 (71) Mult Cls 0 0 10m SY 2017 473 (30) 51 (53) 7 (41) 17 Ohrespine 5-5mg + LX 8 HAMD17 267 (33) Mult Cls 0 0 0 0 0 0 0 0 0 0	7	NCT00797966	43.9 (10.8)	41 (66.1)	62	ADT + brexpiprazole 0.15	9	MADRS	NA	Multi	CIS	0230
43.7 (11) 0.06(61) 121 AUT + Preobio and Shelton 2005 43.7 (11) 0.01 MM MM Thase 2007 43.3 (11.5) 80 (66.1) 126 AUT + Preobio and Shelton 2005 125 (57.5) Mult Cls 0 Thase 2007 43.3 (10.0) 63 (51.8) 200 0larazapire 5-18mg + FLX 8 MADRS 235 (7.7) Mult Cls 0 Thase 2007 43.3 (10.0) 63 (51.8) 200 0larazapire 5-18mg + FLX 8 MADRS 235 (7.7) Mult Cls 0 Cult W2017 43.3 (10.0) 63 (51.8) 200 0larazapire 5-5mg + FLX 8 MADRS 235 (7.7) Mult Cls Ding SY 2017 445 (9.9) 67 (5.7) 200 0larazapire 5-5mg + FLX 8 MADR 235 (6.1) Mult Cls Ding SY 2017 445 (3.3) 7 (45.1) 7 (4.7) 17 Durazapire 5-5mg + FLX 8 MADR 265 (4.7) Single Unclear Ding SY 2017 45 (51.3) 7 (4.1) <td< td=""><td>ATT (TI) B (66) TZ ALI threeponance 1-2mg M Shelun 2005 275 (107) 86 (57) 121 ALI threeponance 1-2mg M Thase 2007 275 (107) 86 (57) 116 Clanzapher 6-1 8mg + FLX 8 MADRS 285 (73) Mult Cls O Thase 2007 275 (107) 96 (57) 126 Clanzapher 6-1 8mg + FLX 8 MADRS 285 (73) Mult Cls O</td><td></td><td></td><td>44.0 (11.8)</td><td>86 (71.7)</td><td>120</td><td>ADT + brexpiprazole 0.25-0.75mg</td><td></td><td></td><td>NA</td><td></td><td></td><td></td></td<>	ATT (TI) B (66) TZ ALI threeponance 1-2mg M Shelun 2005 275 (107) 86 (57) 121 ALI threeponance 1-2mg M Thase 2007 275 (107) 86 (57) 116 Clanzapher 6-1 8mg + FLX 8 MADRS 285 (73) Mult Cls O Thase 2007 275 (107) 96 (57) 126 Clanzapher 6-1 8mg + FLX 8 MADRS 285 (73) Mult Cls O			44.0 (11.8)	86 (71.7)	120	ADT + brexpiprazole 0.25-0.75mg			NA			
Shefton 2005 22:5 (1):1 96 (57.1) 145 Ditr Fragenoe 23:5 (7.5) Milt Cis 24 Cis 25 Milt Cis 26 27 65 75 Milt Cis 26 75 Milt Cis 26 76<	Shelton 2005 #23.5(1:0) #36 (5:1) 142 Ditar Fraeebo (12, 4) RMADRS 228.5(7.5) MMI CS Thase 2007 #37 (10) 103 (72.5) 142 PiX + Placebo (13, 4) PiX + Placebo (13, 4) 28.4 (7.3) MMI CS 29.7 (5.9) MMI CS Thase 2007 #37 (10) 103 (72.5) 142 PiX + Placebo (13, 4) PiX + Placebo (13, 4) PiX + Placebo (14, 4) PiX + Placebo (14, 4) PiX + Placebo (15, 9) MMI CS 29.7 (5.9) MMI CS Ding SY 2017 #35 (9.9) 9 (70.4) 200 Diaraphe 6-16my + PiX 8 MADRS 29.7 (5.9) MMI CS Ding XY 2017 #35 (9.9) 9 (70.4) 200 Diaraphe 6-16my + PiX 8 HAMD MM CS 9			43.7 (11.6)	80 (66.1) 02 (65.1)	121	ADT + brexpiprazole 1–2mg			NA			
These 2007 417 (11) 417 (11) 103 (51) (35 (51) 140 (36 (51) Control (14 (14)) (36 (51) 140 (36 (51) Control (14 (14)) (36 (51) Control (14 (14)) (36 (51) Control (14 (14)) (36 (51) Control (14 (14)) (36 (51) Control (14 (14)) (37 (51) Control (15 (14)) (37 (15) Control (15 (14)) (37 (15) Control (15 (14)) (37 (14)) Control (15 (14)) (37 (14)) Control (16 (14)) (37 (14))	Instantor Array (10) 35(25) 142 Underpred Failury FLX No Array (20) 25(71) Multi Cis 0 CurW 2017 333 (10) 63(51) 200 0larzapine 5-5mg +LX 8 MADFS 333 (15) Multi Cis 0 0 Ding SY 2017 443 (10) 63(51) 200 0larzapine 25-5mg +LX 8 HAMD MA Single Unclear 0	c			(1.00) 20	140	AULT FIAUGUU	С			N. A. 14:	90	
Thase 2007 Transe 2007 <thtranse 2007<="" th=""> <thtranse 2007<="" th=""></thtranse></thtranse>	Thrase 2007 43.3 (103) 43.8 (103) 53 (103) 53 (613) 200 53 (613) Dimested for the form of the f	Ö		(7101) C.74 (711 0)	90 (07.1) 103 (72 5)	140	Ularizapirie o-izirig + rLA El Y - Discebo	Ø	INIAURA	(C. 1) C.07	MULLI	UIS	0000
Insector 438 (100) 53 (13) 50 (13)	Theoretory 438 (10) 53 (6) 200 Extraction of a second seco	o	There 2007	43.3 (11.0)	63 (61 8)	241	ΓLA ∓ ΓΙαύσμο Olsnzanine 6_18ma → ELY	α	MADRS	20.5 (7.1)	NALLI+i	٥Lo	AAEA
Thase 2007 45.3 (9.5) 69 (70.4) 200 Olarzapine 6-18 mg + FLX 8 MADRs 30.6 (6.1) Multi Cls Cls <th< td=""><td>Thase 2007 453 (3-) 69 (70,4) 200 Olarzapine 6–18mg + FLX 8 MADRs 30.6 (61) Mult Cls Ol Ding SY 2017 74.5 (3-) 6 (35.7) 206 Diarzapine 6–18mg + FLX 8 HAMD 30.1 (5-) Mult Cls Oi Ding SY 2017 74.15 74.11 17 Olarzapine 25–5mg + FLX 8 HAMD M Single Unclear 6 Ding SY 2017 47.4 (3.9) 13 (40.6) 32 Olarzapine 25–5mg + FLX 8 HAMD-17 26.1 (3.7) Single Unclear 6 Dong KY 2015 456 (1.3) 46 (51.1) 90 Olarzapine 25–5mg + FLX 8 HAMD-17 26.1 (3.7) Single Unclear 6 Dong KY 2016 456 (1.3) 47 (52.2) 90 Diarzapine 25–5mg + FLX 8 HAMD M</td><td>ה</td><td>111995 2001</td><td>44.8 (10.0)</td><td>63 (61.8)</td><td>206</td><td>FLX + Placebo</td><td>D</td><td></td><td>29.7 (6.9)</td><td>ואומונו</td><td>20</td><td>0000</td></th<>	Thase 2007 453 (3-) 69 (70,4) 200 Olarzapine 6–18mg + FLX 8 MADRs 30.6 (61) Mult Cls Ol Ding SY 2017 74.5 (3-) 6 (35.7) 206 Diarzapine 6–18mg + FLX 8 HAMD 30.1 (5-) Mult Cls Oi Ding SY 2017 74.15 74.11 17 Olarzapine 25–5mg + FLX 8 HAMD M Single Unclear 6 Ding SY 2017 47.4 (3.9) 13 (40.6) 32 Olarzapine 25–5mg + FLX 8 HAMD-17 26.1 (3.7) Single Unclear 6 Dong KY 2015 456 (1.3) 46 (51.1) 90 Olarzapine 25–5mg + FLX 8 HAMD-17 26.1 (3.7) Single Unclear 6 Dong KY 2016 456 (1.3) 47 (52.2) 90 Diarzapine 25–5mg + FLX 8 HAMD M	ה	111995 2001	44.8 (10.0)	63 (61.8)	206	FLX + Placebo	D		29.7 (6.9)	ואומונו	20	0000
445 (9.9) 67 (55.7) 206 FLX + Placebo 301 (5.9) 67 (5.7) Single Unclear Ding SY 2017 477 (3.9) 13 (40.0) 32 Olarzapine 2.5-5mg + FLX 8 HAMD-17 261 (3.7) Single Unclear Dong KY 2016 465 (1.3) 12 (37.5) 32 Olarzapine 2.5-5mg + FLX 8 HAMD-17 261 (3.7) Single Unclear Dong KY 2016 465 (1.3) 12 (37.5) 32 Olarzapine 2.5-5mg + FLX 8 HAMD M Single Unclear Duw 2017 NA NA 45 Olarzapine 5.5-5mg + FLX 8 HAMD N Single Unclear Duw 2017 NA NA A 55 (4.1) 90 Olarzapine 2.5-5mg + FLX 8 HAMD N N Single	Cui Yu 2017 34.5 (9.9) 67 (65.7) 206 FLX + Placebo 30.1 (5.9) Single Unclear 6 Ding SY 2017 37.5 (3.1) 7 (41.1) 17 Diazapine 2.5-5mg + FLX 8 HAMD NM Single Unclear 6 Ding SY 2017 37.5 (3.1) 17 (41.1) 17 Diazapine 2.5-5mg + FLX 8 HAMD-17 26.1 (3.7) Single Unclear 6 Dong KY 2016 455 (1.3) 13 (40.6) 32 0larzapine 2.5-5mg + FLX 8 HAMD NM M 6 6 11 7 267 (3.9) Single Unclear 6 Du W 2017 NA NA A 55 14.4 8 HAMD NM Single Unclear 6 Du W 2017 NA NA A 55 14.4 Single Unclear 6 M NA NA A 56 10 26.1 (3) Single Unclear 6 M NA		Thase 2007	45.3 (9.5)	69 (70.4)	200	Olanzapine 6–18mg + FLX	8	MADRS	30.6 (6.1)	Multi	CIs	(10, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0
Cui YN 2017 37.5 (3.1) 7 (41.1) 17 Olarzapire 2.5-5mg + FLX 8 HAMD NA Single Unclear 39.2 (3.3) 6 (55.2) 17 FLX + Placebo NA NA Single Unclear 39.2 (3.3) 13 (406) 32 Olarzapire 2.5-5mg + FLX 8 HAMD-17 26.1 (3.7) Single Unclear 46.9 (3.7) 12 (37.5) 32 Olarzapire 2.5-5mg + FLX 8 HAMD NA 56.9 Unclear 46.5 (1.3) 47 (52.2) 90 Olarzapire 2.5-5mg + FLX 8 HAMD NA 56.9 Unclear MA MA 45 Olarzapire 2.5-5mg + FLX 8 HAMD NA 56.4 (3) Single Unclear MA NA 45 Olarzapire 2.5-5mg + FLX 8 HAMD NA Single Unclear MA NA A4 5 FLX + Placebo NA 37.1 (4.9) Single Unclear FU J 2018 FU 1275) 90 Olarz	Cui YN 2017 37.5 (3.1) 7 (41.1) 17 Olarzaphe 2.5-5mg + F/X 8 HMID M Single Unclear 6 Ding SY 2017 39.2 (3.3) 6 (3.5.2) 17 F(X + Placebo M Single Unclear 6 Ding SY 2017 45.9 (3.7) 13 (40.6) 32 F(X + Placebo M Single Unclear 6 Dong KY 2016 49.5 (2.6) 46 (51.1) 12 (37.5) 32 F(X + Placebo M M Single Unclear 6 Dun W 2017 NA NA 45 Olarzapine 2.5-5mg + F/X 8 HAMD M Single Unclear 6 Dun W 2017 NA NA 45 Olarzapine 2.5-5mg + F/X 8 HAMD M Single Unclear 6 Duan W 2017 NA NA 45 Olarzapine 2.5-5mg + F/X 8 HAMD M Single Unclear 6 Duan W 2017 NA NA NA Single Unclear			44.5 (9.9)	67 (65.7)	206	FLX + Placebo			30.1 (5.9)			
Ding SY 2017 33.2 (3.3) (3.6) (3.7) (3.6) (3.7) (3.6) (3.7) (3.6) (3.7) (3.6) (3.7) (3.6) (3.6) (3.7) (3.6) (3	Ding SY 2017 312. (3.3) (3.2.3) 1.0 (3.5.4) (3.6) 1.1 (A + Hacebo (3.7) I.A + Hacebo (3.6) I.A + Hacebo (3.7) I.A + Hacebo (3.6) I.A + Hacebo (3.7) I.A + Haceb	10	Cui YN 2017	37.5 (3.1)	7 (41.1)	17	Olanzapine 2.5–5mg + FLX	ω	HAMD	NA	Single	Unclear	00
Ding SY 2017 47.4 (3.9) 13 (40.6) 32 Olarazine 25-5mg +LX 8 HAMD-17 26.1 (3.7) Single Unclear Dong KY 2016 46.9 (3.7) 12 (37.5) 32 Olarazine 25-5mg +LX 8 HAMD 26.7 (3.9) Single Unclear Dong KY 2016 45.5 (2.6) 47 (52.1) 90 Olarazine 25-5mg +LX 8 HAMD NA Single Unclear MA NA NA NA 55 (4.1) 90 Olarazine 25-5mg +FLX 8 HAMD 36.5 (4.7) Single Unclear Du W 2017 NA NA NA 55 (4.1) 90 Olarazine 25-5ing +FLX 8 HAMD 36.4 (4.5) Single Unclear Duan W 2021 65 (8) 11 (27.5) 40 Olarazine 25-5ing +FLX 8 HAMD 36.4 (4.5) Single Unclear Fu J 2018 41.26 (6.1) 26 (40.6) 64 Olarazine 2.5-5ing +FLX 8 HAMD NA Single Unclear Fu J 2018 <td< td=""><td>Ding SY 2017 47.4 (3.9) 13 (40.6) 32 Olarzapine 2.5-5mg + HX 8 HAMD-17 26.1 (3.7) Single Unclear 6 Dong KY 2016 49.5 (2.6) 12 (37.5) 32 FLX + Placebo 8 HAMD-17 26.1 (3.9) Single Unclear 6 Du W 2017 NA NA NA 8 HAMD NA Single Unclear 6 Du W 2017 NA NA NA A 55 (1.3) 90 FLX + Placebo 8 HAMD NA Single Unclear 6 Du W 2021 65 (8) 11 (27.5) 90 FLX + Placebo 8 HAMD NA Single Unclear 6 Fu J 2018 41 (25 (3.9) 11 (27.5) 40 El X + Placebo 8 HAMD NA Single Unclear 6 6 Unclear 6 6 Unclear 6 6 Unclear 6 6 0 6 0 6 6 1</td><td></td><td></td><td>39.2 (3.3)</td><td>0 (35.2)</td><td>/1</td><td></td><td></td><td></td><td>NA</td><td></td><td></td><td></td></td<>	Ding SY 2017 47.4 (3.9) 13 (40.6) 32 Olarzapine 2.5-5mg + HX 8 HAMD-17 26.1 (3.7) Single Unclear 6 Dong KY 2016 49.5 (2.6) 12 (37.5) 32 FLX + Placebo 8 HAMD-17 26.1 (3.9) Single Unclear 6 Du W 2017 NA NA NA 8 HAMD NA Single Unclear 6 Du W 2017 NA NA NA A 55 (1.3) 90 FLX + Placebo 8 HAMD NA Single Unclear 6 Du W 2021 65 (8) 11 (27.5) 90 FLX + Placebo 8 HAMD NA Single Unclear 6 Fu J 2018 41 (25 (3.9) 11 (27.5) 40 El X + Placebo 8 HAMD NA Single Unclear 6 6 Unclear 6 6 Unclear 6 6 Unclear 6 6 0 6 0 6 6 1			39.2 (3.3)	0 (35.2)	/1				NA			
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65.5 (9.5) 12 (30) 40 FLX + Placebo 36.84 (4.53) Fu J 2018 41.25 (5.18) 26 (40.6) 64 Olanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear 40.56 (6.04) 27 (42.1) 64 FLX + Placebo NA Single Unclear Guo L 2015 49.5 (2.6) 46 (51.1) 90 Olanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear Hu HT 2016 NA NA NA NA Single Unclear Hu HT 2016 NA NA NA NA Single Unclear Hu HT 2016 NA NA A7 Olanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear Huang XJ 2021 38.79 (5.37) 24 (58.5) 41 Olanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear 38.83 (5.42) 23 (5.1) 41 Olanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear <	Fu J 2018 65.5 (9.5) 12 (30) 40 FLX + Placebo 36.34 (4.53) Fu J 2018 41.25 (5.18) 26 (40.6) 64 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear 6 duo L 2015 49.5 (5.6) 27 (42.1) 64 FLX + Placebo NA NA Single Unclear 6 Hu HT 2016 NA NA 747.1) 90 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear 6 Hu HT 2016 NA NA NA A7 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear 6 Hu HT 2016 NA NA NA A7 FLX + Placebo NA NA Single Unclear 6 Huang XJ 2021 38.79 (5.37) 24 (58.5) 41 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear 6 NA NA NA NA 47 FLX + Placebo NA NA Single Unclear 6 10anzapine 2.5-5mg + FLX </td <td>14</td> <td>Duan W 2021</td> <td>65 (8)</td> <td>11 (27.5)</td> <td>40</td> <td>Olanzapine 2.5-15mg + FLX</td> <td>8</td> <td>HAMD</td> <td>36.85 (4.44)</td> <td>Single</td> <td>Unclear</td> <td>200</td>	14	Duan W 2021	65 (8)	11 (27.5)	40	Olanzapine 2.5-15mg + FLX	8	HAMD	36.85 (4.44)	Single	Unclear	200
Fu J 2018 41.25 (5.18) 26 (40.6) 64 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear 40.56 (6.04) 27 (42.1) 64 FLX + Placebo NA Single Unclear Guo L 2015 49.5 (2.6) 46 (51.1) 90 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear Hu HT 2016 NA NA NA 77 (52.2) 90 FLX + Placebo NA Single Unclear Hu HT 2016 NA NA A7 FLX + Placebo NA NA NA Single U	Fu J 2018 41.25 (5.18) 26 (40.6) 64 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear © duo L 2015 49.5 (6.04) 27 (42.1) 64 FLX + Placebo NA NA Single Unclear © duo L 2015 49.5 (2.6) 46 (51.1) 90 Olarzapine 2.5-5mg + FLX 8 HAMD NA NA Single Unclear © Hu HT 2016 NA NA NA 47 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear © Hu HT 2016 NA NA NA 47 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear © Huang XJ 2021 38.79 (5.37) 24 (58.5) 41 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear © Huang XJ 2021 38.83 (5.42) 23 (56.1) 41 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear © 10 and XJ 2021 38.83 (5.42) 23 (56.1) 41 Olarzapine			65.5 (9.5)	12 (30)	40	FLX + Placebo			36.84 (4.53)	I		
40.56 (6.04) 27 (42.1) 64 FLX + Placebo NA Guo L 2015 49.5 (2.6) 46 (51.1) 90 0lanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear Hu HT 2016 NA NA Single Unclear NA NA Single Unclear Hu HT 2016 NA NA A7 0lanzapine 2.5-5mg + FLX 8 HAMD NA NA NA NA NA A7 0lanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear Hu HT 2016 NA NA NA A7 FLX + Placebo NA Single Unclear Huang XJ 2021 38.37 (5.37) 24 (58.5) 41 Olanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear 38.83 (5.42) 23 (56.1) 41 FLX + Placebo NA NA Single Unclear	40.56 (6.04) 27 (42.1) 64 FLX + Placebo NA Guo L 2015 49.5 (2.6) 46 (51.1) 90 Olarzapine 2:5-5mg + FLX 8 HAMD NA Single Unclear @ Hu HT 2016 NA NA NA NA Single Unclear @ Hu HT 2016 NA NA NA NA Single Unclear @ Hu HT 2016 NA NA NA NA NA Single Unclear @ Hu HT 2016 NA NA NA NA NA Single Unclear @ Huang XJ 2021 38.79 (5.37) 24 (58.5) 41 Olarzapine 2.5-5mg + FLX 8 HAMD NA NA NA Na NA NA NA NA NA NA Single Unclear @ Huang XJ 2021 38.83 (5.42) 23 (56.1) 41 FLX + Placebo NA NA NA Single Unclear @ 38.83 (5.42) 23 (56.1) 41 FLX + Placebo NA NA <t< td=""><td>15</td><td>Fu J 2018</td><td>41.25 (5.18)</td><td>26 (40.6)</td><td>64</td><td>Olanzapine 2.5-5mg + FLX</td><td>œ</td><td>HAMD</td><td>NA</td><td>Single</td><td>Unclear</td><td>20</td></t<>	15	Fu J 2018	41.25 (5.18)	26 (40.6)	64	Olanzapine 2.5-5mg + FLX	œ	HAMD	NA	Single	Unclear	20
Guo L 2015 49.5 (2.6) 46 (51.1) 90 0lanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear Hu HT 2016 46.5 (1.3) 47 (52.2) 90 FLX + Placebo NA NA Single Unclear Hu HT 2016 NA NA 47 0lanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear Hu HT 2016 NA NA 47 0lanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear Huang XJ 2021 38.79 (5.37) 24 (58.5) 41 0lanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear Huang XJ 2021 38.83 (5.42) 23 (56.1) 41 FLX + Placebo NA Single Unclear	Guo L 2015 49.5 (2.6) 46 (51.1) 90 Olarzapire 2.5-5mg + FLX 8 HAMD NA Single Unclear 6 Hu HT 2016 NA 47 (52.2) 90 FLX + Placebo NA Single Unclear 6 Hu HT 2016 NA NA NA Single Unclear 6 Hu HT 2016 NA NA NA 47 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear 6 NA NA NA NA NA A 7 FLX + Placebo NA NA Single Unclear 6 Huang XJ 2021 38.73 (5.42) 23 (56.1) 41 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear 6 Huang XJ 2021 38.83 (5.42) 23 (56.1) 41 FLX + Placebo NA NA Single Unclear 6 38.83 (5.42) 23 (56.1) 41 FLX + Placebo NA NA Single Unclear 6			40.56 (6.04)	27 (42.1)	64	FLX + Placebo			NA			
Hu HT 2016 WA NA NA 47 Olanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear NA NA NA 47 FLX + Placebo NA Single Unclear Huang XJ 2021 38.79 (5.37) 2.4 (58.5) 4.1 Olanzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear 38.83 (5.42) 2.3 (56.1) 4.1 FLX + Placebo NA Single Unclear	Hu HT 2016 40.5 (1) 41 (32.1.) 50 FLX Fraceuo NA NA NA 71 72 (36.5) 41 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear C Huang XJ 2021 38.79 (5.37) 24 (58.5) 41 Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear C 38.83 (5.42) 23 (56.1) 41 FLX + Placebo NA Single Unclear C	16	Guo L 2015	49.5 (2.6)	46 (51.1)	06	Olanzapine 2.5–5mg + FLX	ω	HAMD	NA	Single	Unclear	90
Huang XJ 2021 38.79 (5.37) 24 (58.5) 41 FLX + Placebo NA Onlyce Unceater NA NA Onlyce Unceater NA NA Onlyce Unceater NA Single Unclear Starts 23.83 (5.42) 23 (56.1) 41 FLX + Placebo NA Single Unclear NA Single Unclear	Huang XJ 2021 38.33 (5.42) 23 (56.1) 41 FLX + Placebo NA Olarzapine 2.5-5mg + FLX 8 HAMD NA Olarzapine 2.5-5mg + FLX 8 HAMD NA Single Unclear (1 1 1 1 1 2 4 1 1 1 1 2 4 1 1 1 1 1 2 4 1 1 1 1	71	HII 1 2016		47 (JZ:Z)	30	ГЕЛ + ГIAUEJU Папталіра 2 Б. Бта - EI V	a			Cinalo	llnoloar	90
Huang XJ 2021 38.79 (5.37) 24 (58.5) 41 Olarizapine 2.5–5mg + FLX 8 HAMD NA Single Unclear 38.83 (5.42) 23 (56.1) 41 FLX + Placebo 8 HAMD NA Single Unclear	Huang XJ 2021 38.79 (5.37) 24 (58.5) 41 Olanzapine 2.5–5mg + FLX 8 HAMD NA Single Unclear @ 38.83 (5.42) 23 (56.1) 41 FLX + Placebo NA	2		AN	AN AN	47	Planzaprile 2:3-3111g + 1 LA FLX + Placebo	D	סואוצוו	NA	olligie	חוננופמו	9
38.83 (5.42) 23 (56.1) 41 FLX + Placebo	38.83 (5.42) 23 (56.1) 41 FLX + Placebo	18	Huang XJ 2021	38.79 (5.37)	24 (58.5)	41	Olanzapine 2.5-5mg + FLX	8	HAMD	NA	Single	Unclear	6
	(Centinized)			38.83 (5.42)	23 (56.1)	41	FLX + Placebo			NA			

Table 1

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Table 1	(Continued)
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Application Bandle with the sector of the sec		(
Jac OM 2015 g_{12} g_{12}		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) 36.9 (9.7)	22 (44) 23 (46)	50	Olanzapine 2.5–5mg + FLX FLX + Placebo	8	HAMD	NA	Single	Unclear	0
	20	Li YY 2017	37.13 (1.6) 37.15 (1.62)	20 (46.5) 21 (48.8)	43	Olanzapine 2.5–5mg + FLX FLX + Placebo	8	HAMD	NA NA	Single	Unclear	200
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	21	Li Y 2017	41.7 (5.3) 42.1 (5.2)	21 (43.75) 20 (41.7)	- 48 48	Olanzapine 2.5–5mg + FLX FI X + Placebo	8	HAMD	25.9 (1.7) 26.1 (1.9)	Single	Unclear	30
Inv Min Sig Description Sig Description Description <thdescription< th=""> Description</thdescription<>	22	Liang LJ 2014	36.8 (2.6) 35.8 (2.8)	23 (43.3) 20 (37_7)	53	Olanzapine 2.5–5mg + FLX FI X + Placeho	80	HAMD	NA	Single	Unclear	0
PutMC201 2276(43) 324/0 60 Dummer23-Sing + LX 18 Hold - 17 2226(33) Singe Uncer Sin Y 2000 M 10(63) 20 Dummer23-Sing + LX 8 Hold - 17 2823(33) Singe Uncer Sing Y 2010 M 10(63) 22 Dummer23-Sing + LX 8 Hold - 1 2823(33) Singe Uncer Sing Y 2010 M 10(63) 12(63) 0 Dummer23-Sing + LX 8 Hold - 1 2823(33) Singe Uncer Many J 2017 M 365(10) 18(73) 0 Dumerative 2-Sing + LX 8 Hold - 1 283(33) Singe Uncer Many J 2017 M 365(10) 18(73) 0 Dumerative 2-Sing + HX 8 Hold - 1 Singe Uncer Many J 2017 M 365(10) 13(73) 17 Hold - 1 Singe Uncer Singe Uncer Many J 2017 M 365(10) 13(73) 10 Mony Singe<	23	Liu YP 2012	NA NA	NA	50	Olanzapine 2.5–5mg + FLX	ω	HAMD-17	NA	Single	Unclear	330
Silv 2000 With 200 10(5)/5 20 Operating 27:ent + LX 8 HAND 55:50/5 Single Under Un	24	Pu MX 2017	42.26 (4.42) 42.28 (4.46)	32 (47.0) 31 (45.5)	08 89	I LAA + Haccoo Olanzapine 2.5–5mg + FLX FI X + Placeho	8	HAMD-17	28.84 (3.29) 28.82 (3.36)	Single	Unclear	00
Sing 2018 $g_{16}(g_{10})$ $10^{17}(5)$ 00 Discretive 2.5-fing + 1X 8 HMID M Single Under $Warg J2017$ <td< td=""><td>25</td><td>Shi Y 2020</td><td>NA</td><td>10 (45.4) 11 (50)</td><td>22</td><td>Olanzapine 2.5mg + FLX Fl X + Placeho</td><td>80</td><td>HAMD</td><td>37.44 (4.28)</td><td>Single</td><td>Unclear</td><td>9</td></td<>	25	Shi Y 2020	NA	10 (45.4) 11 (50)	22	Olanzapine 2.5mg + FLX Fl X + Placeho	80	HAMD	37.44 (4.28)	Single	Unclear	9
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	26	Song Y 2018	48.6 (9.4) 47 2 (8 q)	19 (47.5) 18 (45)	40	Olanzapine 2.5–5mg + FLX FI X + Placeho	8	HAMD	NA	Single	Unclear	00
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Bernan 2009 45, (10) 338 (73) 74 Frankanov Mana 236 (53) Mult Cis Reman 2007 455 (11) 11 (56) 137 700 (51) 715 (50) 715 (50) 715 (50) 715 (50) 716 (50) 716 (50) 716 (50) 716 (51) <td>28</td> <td>Wang J 2017</td> <td>NA</td> <td>19 (44.19)</td> <td>4 6 7 7</td> <td>Olanzapine 2.5–5mg + FLX</td> <td>8</td> <td>HAMD</td> <td>NA NA</td> <td>Single</td> <td>Unclear</td> <td>3</td>	28	Wang J 2017	NA	19 (44.19)	4 6 7 7	Olanzapine 2.5–5mg + FLX	8	HAMD	NA NA	Single	Unclear	3
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Kamilina 2013 332 (1) 33 (1) 33 (3) (1) 33 (37) (1	30	Berman 2007	45.5 (10.6)	112 (61.5) 112 (61.5)	182	praceto + ADT Aripiprazole2–20mg + ADT	9	MADRS	26.0 (6.1) 26.0 (6.1)	Multi	CIs	02346
Sol (32)	31	Kamijima 2013	44.2 (10.9) 39.2 (9.1)	73 (37.1)	197	placebo + AU I Aripiprazole 3mg + ADT Arisiprazole 3 1 Ema - ADT	9	MADRS	25.2 (7.2) 25.2 (7.2)	Multi	Cls	02460
Andminat.Cuto 355 (11:6) 7 (3) <td>C</td> <td>0100</td> <td>38.7 (9.2)</td> <td>80 (41.0) 70 (00 0)</td> <td>195 195</td> <td>Aupprazore 3–131119 + AUT placebo + ADT</td> <td>c</td> <td></td> <td>25.5 (7.4)</td> <td>111. IA</td> <td>č</td> <td></td>	C	0100	38.7 (9.2)	80 (41.0) 70 (00 0)	195 195	Aupprazore 3–131119 + AUT placebo + ADT	c		25.5 (7.4)	111. IA	č	
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Liang XL 2020 Turble for the constraint of t	34	Li XX 2020	41.29 (6.48) 42.15 (7.15)	26 (43.3) 27 (53 2)	60 60	Aripiprazole 5–10mg + ADT	8	HAMD-17	36.44 (2.97) 37 56 (3.01)	Single	Unclear	Ð
Wang KP 2020 386.27 (5) 386.2 (5) 39.35 (6.24) 11 (4.37) (5.7.13) 32 37.13 (1.42) 32 Aniporation - 20mg + ADT 39.35 (6.24) 8 (5.7.1) HAMD-17 26.49 (1.31) 27.13 (1.42) Single Unclear Zhang J 2012 33.55 (6.24) 15 (46.8) 32 Anipiprazole 5–15 mg + ADT 8 HAMD-17 26.34 (1.31) Single Unclear Zhang J 2012 33.55 (6.24) 15 (46.8) 32 Anipiprazole 5–15 mg + ADT 8 HAMD 29.3 (3.3) Single Unclear NCT01111552 NA NA NA NA NA Multi Cls NCT01111552 NA NA NA NA NA Multi Cls NCT01111555 NA NA <t< td=""><td>35</td><td>Liang XL 2020</td><td>40.5 (9.9) 30 7 (8 7)</td><td>16 (51.6) 11 (35.4)</td><td>3 3 3</td><td>Aripiprazole 10–15mg + ADT</td><td>9</td><td>HAMD</td><td>27.9 (4.1) 28 2 (3 7)</td><td>Single</td><td>Unclear</td><td>207</td></t<>	35	Liang XL 2020	40.5 (9.9) 30 7 (8 7)	16 (51.6) 11 (35.4)	3 3 3	Aripiprazole 10–15mg + ADT	9	HAMD	27.9 (4.1) 28 2 (3 7)	Single	Unclear	207
Zhang J 2012 Use of the constraint of	36	Wang KP 2020	38.62 (5.75) 30.35 (6.74)	14 (43.7) 15 (46.8)	32	Aripiprazole10–20mg + ADT	ω	HAMD-17	26.49 (1.31) 27 13 (1.40)	Single	Unclear	3
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NCT01111565 NA NA NA NA NA NA NA NA Multi CIS NCT01111539 NA NA NA NA NA NA NA Multi CIS NCT01111539 NA NA NA NA NA NA NA NA Multi CIS NCT0111539 NA Multi CIS S6.6.6.0 S6.6.6.0 S6.6.6.0 S6.6.6.0 Multi CIS S6.6.6.0 S6.6.6.0 S6.6.6.0 S6.6.6.0 Multi CIS S6.6.6.0 Multi CIS S6.6.6.0 S6.6.6.0 <	38	NCT01111552	NA NA	NA NA	3 23 6	Aripiprazole 3–12mg + ADT	9	MADRS	NA NA	Multi	CIs	(J) (D)
NCT01111539 NA NA NA NA NA NA NA NA NA Multi Cls NCT01111539 NA NA NA NA NA NA Multi Cls NA SB.4(5.6) Nulti Cls SB.4(5.6) Nulti Cls SB.4(5.5) Na SB.4(5.5) SB.4(5.5) NA	39	NCT01111565	AN AN	AN N	16	Aripiprazole 3–12mg + ADT	9	HAMD-17	AN NA	Multi	CIS	1450
Bauer 2009 44.8 (10.4) 104 (65.0) 160 Placebo + ADT 6 NA 28.2 (5.6) Multi Cls 46.0 (10.1) 115 (69.3) 166 Quetiapine XR 150mg 6 NA 28.2 (5.6) Multi Cls 45.5 (11.1) 110 (68.3) 161 Quetiapine XR 300mg 28.4 (5.5) 28.4 (5.5)	40	NCT01111539	AN N	AN N	28 -4	Aripiprazole 6–12mg + ADT	9	HAMD-17	NA NA	Multi	CIS	1450
115 (e9.3) 166 Quettapine XR 150mg 110 (68.3) 161 Quettapine XR 300mg	41	Bauer 2009	44.8 (10.4)	104 (65.0)	160	Placebo + ADT	9	NA	28.2 (5.6)	Multi	CIs	000000
			46.0 (10.1) 45.5 (11.1)	115 (69.3) 110 (68.3)	166 161	Quetiapine XK 150mg Quetiapine XR 300mg			28.6 (5.4) 28.4 (5.5)			

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(Continued)

	Study name	(SD)	remale n (%)	No. randomised	Drug (dose of synergist(min- max,mg, daily))	Uuration (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	9	MADRS	27.6 (5.5)	Multi	Cls	023667
43	McIntyre 2007	45.9 (11.0 44.3 (11.3) 44 (10)	1 09 (76.2) 1 06 (72.6) 18 (65)	143 146 29	Quetiapine XR 150mg + ADT Quetiapine XR 300mg + ADT Quetiapine XR 50–	ω	HAM-D17	27.2 (5.2) 27.6 (5.0) 23.4 (3.0)	Single	Unclear	() () () () () () () () () () () () () (
44	Moica 2018	45 (12) 40.27	17 (59) 26 (72.2)	29 36	600mg + ADT Placebo + ADT Quetiapine XR 50–	œ	HAM-D17	23.2 (2.2) 22.17 (3.23)	Single	Unclear	©
45	Duan CF 2012	39.25 32.5 (5.7)	28 (77.7) 18 (60.0)	36 30	150mg + ADT Placebo + ADT Quetiapine XR 50-	9	HAMD	24.61 (4.19) NA	Single	Unclear	9 C
46	Duan J 2017	32.8 (5.6) 39.1 (6.7)	19 (63.3) 22 (33.8)	30 65	300mg + ADT placebo + ADT Quetiapine XR 50-	œ	HAMD	NA 51.2 (12.3)	Single	Unclear	0 0
47	Gao DQ 2020	38.2 (6.6) 44.64 (18.32)	29 (44.6) 31 (62.0)	65 50	/ 50mg + AUT placebo + ADT Quetiapine XR 50-	8	HAMD	50.9 (11.6) 28.62 (2.66)	Single	Unclear	2 © (1)
48	Liu L 2006	45.58 (16.77) 31.3 (6.5)	29 (58.0) 16 (48.4)	50 33	150mg + AUI Placebo + ADT Quetiapine XR 100-	9	HAMD	29.08 (2.83) 28.4 (5.3)	Single	Unclear	0 ©
49	Peng BQ 2017	30.2 (6.3) 45.74 (3.85)	14 (51.8) 19 (44.1)	27 43	400mg + ADT placebo + ADT Quetiapine XR 100-	ω	HAMD	29.6 (4.9) NA	Single	Unclear	@ Ø
50	Shi QS 2021	45.25 (3.58) 44.27 (3.72)	20 (46.5) 21 (61.7)	43 34	400mg + ADT placebo + ADT Quettapine XR 50-	ω	MADRS	NA 33.02 (2.41)	Single	Unclear	000
51	Zhang CL 2015	44.31 (3.74) 32.01 (11.98)	20 (58.8) 24 (45.1)	34 52	150mg + ADT placebo + ADT Quetiapine XR 100-	œ	HAMD-24	32.97 (2.38) 57.41 (13.74)	Single	Unclear	20 0
52	Zhang HT 2014	33.56 (13.10) 32.6 (7.3)	29 (55.7) 17 (42.5)	52 40	300mg + AUT placebo + ADT Quetiapine XR 50-	œ	HAMD	52.57 (17.48) 33.78 (5.63)	Single	Unclear	() ()
53	Zhou P 2019	32.8 (7.6) 39.01 (6.8)	16 (40.0) 13 (43.3)	40 30	250mg + ADT placebo + ADT Quettapine XR 50-	Ø	HAMD	34.23 (6.23) 51.3 (11.7)	Single	Unclear	() () ()
54	Shelton 2001	38.25 (6.7) NA	12 (40) NA	10 10 10	600mg + ADT placebo + ADT Olanzapine 5-20mg + FLX Fl X + Placebo	8	MADRS	51.1 (11.8) NA NA	Single	Cls	(12)
55	Corya 2006	AN N	AN	243	Olanzapine 7.9mg + FLX	12	MADRS	AN N	Multi	CIS	12345
56	Fava 2012	45.06 (11.34)	37 (66.07) 108 (63.91)	00 56 169	Aripiprazole 2 mg + ADT placebo + ADT	4	MADRS	AN	Multi	CIS	1245

Table 1

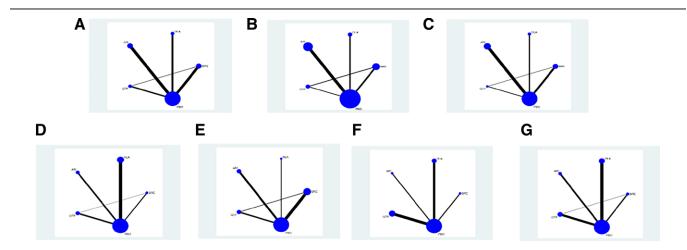


Figure 2. Network of eligible comparisons for 7 outcomes. (A) (depressive symptom score (MADRS)); (B) (acceptability); (C) (tolerability); (D) (response rate); (E) (remission rate); (F) (depressive symptom score (HAMD)); (G) (adverse events incidence rate). The width of the lines is proportional to the 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 sympto	om scores(SMD[95%,CI])	Comparison	Resp	onse 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)	РВО

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 discontin	nuation(RR[95%,CI])	Comparison	Side-effect di	scontinuation(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 = queti-apine, 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.

	The mean MADRS tota baseline tu	The mean change in MADRS total score from baseline to endpoint	All-cause discontinuation	continuation	side-effects Discontinuation	fects nuation	Remission rate	on rate	Adverse events incidence rate	ts incidence e	Response rate	se rate	The mean change in HAMD total score from baseline to endpoint	nange I score ne to it
Comparision	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank
BRE + ADT	45.1	4	68.1		47.6	с	48.5	С	22.6	4	73.6	2	22.1	4
DLA + ADT	70.5	2	42.6	c	31.6	4	74.6	2	98.4	-	52.4	e	97.1	-
ARI + ADT	54.6	e	41.0	4	52.9	2	81.0	-	9.6	Ð	96.6		73.5	2
QTP + ADT	79.6	, -	40.5	5	18.0	2	45.3	4	43.9	с	27.3	4	50.3	က
PB0 + ADT	0.2	2	57.8	2	99.9	, -	0.5	5	75.5	2	0.0	Ð	7.0	2

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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 D₂ 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

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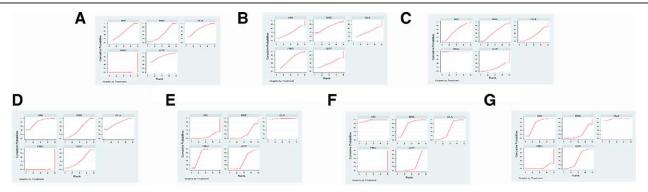


Figure 5. The ranking of TCMIs based on cumulative probability plots and SUCRA. (A) (depressive symptom score (MADRS)), (B) (acceptability), (C) (tolerability), (D) (remission rate), (E) (adverse events incidence rate), (F) (response rate), (G) (depressive symptom score (HAMD)). SUCRA = surface under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