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The augmentative efficacy of second-generation anti-psychotics (SGA) to anti-depressants in treating treatment-resistant depression: a network meta-regression analysis

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Abstract

Background To compare the augmentative efficacy of second-generation anti-psychotics (SGA) to anti-depressants in adult patients with treatment-resistant depression (TRD) adjusting follow-up period and explore the underlying"time window"effects of the regimens.

Methods Databases included Embase, PubMed, Scopus, Cochrane Library and Google Scholars as well as Clinicaltrials.gov from inception to May 15, 2024, for relevant randomized controlled studies (RCTs) were retrieved. The primary endpoint was Montgomery Asberg Depression Rating Scale (MADRS). The secondary endpoint was MADRS response rate. The tertiary endpoints were Clinical Global Impression-severity (CGI-S) and MADRS remission rate. Standard mean difference (SMD) and hazard ratio (HR) were generated by Bayesian network meta-regression (NMR) for pairwise comparisons on dichotomous and consecutive variants, respectively.

Results A total of 23 studies (N = 10679) with 24 augmentation agents were included in the NMR. For the primary endpoint, compared with ADT, aripiprazole 3 - 12 mg/d, brexpiprazole 1 - 3 mg/d, cariprazine 1.5 - 3 mg/d, olanzapine 6 - 12 mg/d and fluoxetine 25 - 50 mg/d combination, and quetiapine XR were significantly effective (SMD ranged from - 0.28 to - 0.114) and their effect sizes were comparable, after adjusting follow-up period, the results resembled the former except for quetiapine XR (SMD = - 0.10, 95%CI: - 0.212 to 0.014). Brexpiprazole 3 mg/d (7.22 weeks), cariprazine 1 - 2 mg/d (2.97 weeks), cariprazine 2–4.5 mg/d (2.81 weeks), cariprazine 3 mg/d (7.16 weeks), olanzapine 6 - 12 mg/d (4.11 weeks) and quetiapine 150 - 300 mg/d (3.89 weeks) showed"time window". For the secondary endpoint, brexpiprazole 3 mg/d and rispridone 0.5 - 3 mg/d was evidently superior to all others (HR ranged from 1.748 to 2.301). For the tertiary endpoints, as for CGI-S, aripiprazole 2 - 20 mg/d, brexpiprazole 2 - 3 mg/d, cariprazine 3 mg/d, olanzapine 6 - 12 mg/d and fluoxetine 25 - 50 mg/d combination, and rispridone 0.5 - 3 mg/d were conspicuously effective compared with ADT (SMD ranged from - 0.438 to - 0.126) and for MADRS remission rate, aripiprazole 2 - 20 mg/d, brexpiprazole 3 mg/d, cariprazine 3 mg/d, rispridone 0.5 - 3 mg/d were conspicuously effective compared with ADT (HR ranged from 0.477 to 3.326).

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Conclusion Holistically considering each endpoint and corresponding "time window", certain SGAs appeared to be efficient augmentation to anti-depressants for TRD, but aripiprazole was relatively more effective and better tolerated.

Keywords Efficacy, Second-generation antipsychotics, Network Meta-regression, Treatment resistant depression, Time window

Introduction

Depression did not come well into the views of the public peculiarly Chinese until the suicide (jumped to his death) conducted by Leslie Cheung, the prestigious singer and actor who had been suffering major depression, on April 1 st, 2003 [1].

In 2019, 7.8% of adults in the US experienced at least 1 major depressive episode; 5.3% (13.1 million) experienced a major depressive disorder (MDD) with severe social function impairment [2]. Coincidentally,"Report on national mental health development in China (2019–2020)"showed that the detection rate of MDD was 7.4% among population with age ranged from 18 to 34 years [3].

Moreover, the COVID- 19 pandemic has led to a sharp increase in the number of people suffering from MDD [4]. The crush of the Covid- 19 in China especially in Shanghai undoubtedly incited numerous underlying depressions [5].

Among individuals meeting criteria for MDD, ≥30% of which even with access to high quality professional health care will eventually progress treatment-resistant depression (TRD) [6].

In terms of treating TRD, the efficacy of secondary-generation antipsychotics (SGA) has been well validated, making them become exclusively pervasive as singular or adjuvant medication for patients with TRD who failed to response to anti-depressive therapy (ADT) regimens [7].

As a milestone in 2010, the first study to investigate SGAs in the treatment of MDD showed aripiprazole, quetiapine, partly also olanzapine and risperidone augmentation therapies beneficial effects compared with ADT [8]. Imperatively, guideline formulated by Canadian Network for Mood and Anxiety Treatments (CANMAT) had incorporated SGAs as TRD remedy in 2016 thereafter [9].

Up to date, the second-generation of antipsychotic agents, namely atypical antipsychotics, comprised amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, etc. [7, 10–12].

Despite that recent meta-analyses have investigated SGAs in treating TRD, insidious confounding factors including treatment period, which was vital in evaluating the effects of SGAs in treating TRD, was not adjusted and the agents included was not comprehensive enough as aforementioned [13, 14]. By adjusting follow-up time, augmentative efficacy can be evaluated more comprehensively to guide treatment regimens such as sequential therapy in the clinic. In addition, the efficacy of augmentative SGA therapy in treatment-resistant depression has been summarized in previous meta-analyses of randomized controlled trials (RCTs), no comprehensive evaluation of different doses of each SGA has been conducted [12, 14–17].

Hence, from the point of prudence, meticulous, comprehensiveness, and precision, we conducted this Bayesian network meta-regression (NMR) analyses to compare the efficacy of SGAs as many as possible in treating TRD and adjust follow-up period.

Materials and methods

Searching strategy

This study was conducted in accordance with the 2020 preferred reporting items for systematic review and meta-analysis (PRISMA) statement [18].

Databases including Embase, PubMed, Scopus, Cochrane Library and Google Scholars as well as Clinicaltrials.gov were retrieved for pertinent articles from inception to May 15, 2024. The MeSH terms were shown in supplementary materials Table 1.

Inclusion criteria

Given the paucity of criteria on TRD in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM- 5) or The International Statistical Classification of Diseases and Related Health Problems 10 th Revision (ICD- 10), we referred to authoritative articles for principles of TRD widely acknowledged.

(1) MDD patients required a minimum of two prior treatment failures and confirmation of prior adequate dose and duration [19].
(2) Randomized controlled studies on SGAs in treating TRD.
(3) The endpoints including at least one of the following: MADRS score; MADRS response rate; CGI-S score and MADRS remission rate.
(4) The dosages of regimens and follow-up period were clearly stated.

Table 1 Matrix of pairwise comparisons on MADRS score for second-generation antipsychotics to augment the efficacy in treating treatment-resistant depression (shown as standard mean difference and 95% confidence intervals)

	ADT	Aripiprazole 3–12 mg/d	Brexpiprazole 1 mg/d	Brexpiprazole 2–3 mg/d	Brexpiprazole 2 mg/d	Brexpiprazole 3 mg/d	Caraprizine 1–2 mg/d	Caraprizine 2–4.5 mg/d
ADT	0	− 0.28 (− 0.487, − 0.078)	− 0.208 (− 0.267, − 0.148)	− 0.272 (− 0.374, − 0.172)	− 0.175 (− 0.278, − 0.075)	− 0.158 (− 0.222, − 0.095)	− 0.022 (− 0.147, 0.108)	− 0.032 (− 0.173, 0.107)
Aripiprazole 3–12 mg/d	0.28 (0.078, 0.487)	0	0.073 (− 0.138, 0.289)	0.008 (− 0.219, 0.239)	0.105 (− 0.122, 0.334)	0.122 (− 0.09, 0.342)	0.26 (0.018, 0.499)	0.249 (0.001, 0.496)
Brexpiprazole 1 mg	0.208 (0.148, 0.267)	− 0.073 (− 0.289, 0.138)	0	− 0.065 (− 0.183, 0.054)	0.032 (− 0.077, 0.141)	0.05 (− 0.014, 0.112)	0.187 (0.046, 0.328)	0.175 (0.024, 0.328)
Brexpiprazole 2–3 mg	0.272 (0.172, 0.374)	− 0.008 (− 0.239, 0.219)	0.065 (− 0.054, 0.183)	0	0.097 (− 0.048, 0.24)	0.114 (− 0.006, 0.233)	0.25 (0.089, 0.414)	0.239 (0.065, 0.412)
Brexpiprazole 2 mg	0.175 (0.075, 0.278)	− 0.105 (− 0.334, 0.122)	− 0.032 (− 0.141, 0.077)	− 0.097 (− 0.24, 0.048)	0	0.017 (− 0.098, 0.134)	0.155 (− 0.007, 0.319)	0.144 (− 0.029, 0.314)
Brexpiprazole 3 mg	0.158 (0.095, 0.222)	− 0.122 (− 0.342, 0.09)	− 0.05 (− 0.112, 0.014)	− 0.114 (− 0.233, 0.006)	− 0.017 (− 0.134, 0.098)	0	0.137 (− 0.003, 0.28)	0.126 (− 0.026, 0.279)
Caraprizine 1–2 mg	0.022 (− 0.108, 0.147)	− 0.26 (− 0.499, − 0.018)	− 0.187 (− 0.328, − 0.046)	− 0.25 (− 0.414, − 0.089)	− 0.155 (− 0.319, 0.007)	− 0.137 (− 0.28, 0.003)	0	− 0.012 (− 0.15, 0.128)
Caraprizine 2–4.5 mg	0.032 (− 0.107, 0.173)	− 0.249 (− 0.496, − 0.001)	− 0.175 (− 0.328, − 0.024)	− 0.239 (− 0.412, − 0.065)	− 0.144 (− 0.314, 0.029)	− 0.126 (− 0.279, 0.026)	0.012 (− 0.128, 0.15)	0
Caraprizine 0.1–0.3 mg	− 0.024 (− 0.258, 0.213)	− 0.305 (− 0.615, 0.007)	− 0.23 (− 0.474, 0.014)	− 0.297 (− 0.551, − 0.039)	− 0.199 (− 0.456, 0.057)	− 0.182 (− 0.424, 0.063)	− 0.045 (− 0.283, 0.197)	− 0.056 (− 0.314, 0.205)
Caraprizine 1.5 mg	0.135 (0.028, 0.24)	− 0.146 (− 0.379, 0.085)	− 0.073 (− 0.196, 0.048)	− 0.137 (− 0.285, 0.009)	− 0.041 (− 0.19, 0.103)	− 0.023 (− 0.148, 0.099)	0.113 (− 0.052, 0.282)	0.102 (− 0.075, 0.278)
Caraprizine 3 mg	0.135 (0.029, 0.242)	− 0.145 (− 0.379, 0.084)	− 0.073 (− 0.195, 0.048)	− 0.138 (− 0.284, 0.009)	− 0.041 (− 0.187, 0.105)	− 0.023 (− 0.148, 0.1)	0.114 (− 0.05, 0.279)	0.103 (− 0.073, 0.276)
Olanzapine 6–12 mg + Fluoxetine 25–50 mg combination	0.248 (0.2, 0.295)	− 0.033 (− 0.243, 0.176)	0.04 (− 0.036, 0.116)	− 0.024 (− 0.136, 0.088)	0.072 (− 0.04, 0.184)	0.09 (0.012, 0.17)	0.227 (0.093, 0.363)	0.216 (0.068, 0.364)
Quetiapine 150–300 mg	0.114 (0.001, 0.229)	− 0.166 (− 0.4, 0.066)	− 0.093 (− 0.223, 0.037)	− 0.158 (− 0.269, − 0.044)	− 0.062 (− 0.211, 0.092)	− 0.044 (− 0.176, 0.086)	0.093 (− 0.075, 0.264)	0.083 (− 0.099, 0.261)
Olanzapine 6–12 mg	0.037 (− 0.011, 0.084)	− 0.244 (− 0.457, − 0.036)	− 0.171 (− 0.246, − 0.096)	− 0.235 (− 0.347, − 0.124)	− 0.139 (− 0.251, − 0.027)	− 0.122 (− 0.2, − 0.042)	0.016 (− 0.119, 0.151)	0.005 (− 0.142, 0.151)
Ziprasidon 160 mg/d	0.196 (− 0.31, 0.702)	− 0.086 (− 0.633, 0.465)	− 0.012 (− 0.521, 0.5)	− 0.077 (− 0.591, 0.444)	0.021 (− 0.501, 0.536)	0.037 (− 0.474, 0.547)	0.173 (− 0.351, 0.702)	0.162 (− 0.363, 0.696)
Ziprasidone 80 mg/d	0.079 (− 0.423, 0.609)	− 0.203 (− 0.737, 0.362)	− 0.127 (− 0.637, 0.403)	− 0.193 (− 0.709, 0.345)	− 0.096 (− 0.612, 0.435)	− 0.079 (− 0.587, 0.453)	0.057 (− 0.466, 0.608)	0.047 (− 0.482, 0.594)
	Caraprizine 0.1–0.3 mg/d	**Caraprizine 1.5 mg/d**	**Caraprizin 3 mg/d**	**Olanzapine 6–12 mg + Fluoxetine 25–50 mg combination/d**	**Quetiapine 150–300 mg/d**	**Olanzapine 6–12 mg/d**	**Ziprasidone 160 mg/d**	**Ziprasidon 80 mg/d**
ADT	0.024 (− 0.213, 0.258)	− 0.135 (− 0.24, − 0.028)	− 0.135 (− 0.242, − 0.029)	− 0.248 (− 0.295, − 0.2)	− 0.114 (− 0.229, − 0.001)	− 0.037 (− 0.084, 0.011)	− 0.196 (− 0.702, 0.31)	− 0.079 (− 0.609, 0.423)
Aripiprazole 3–12 mg/d	0.305 (− 0.007, 0.615)	0.146 (− 0.085, 0.379)	0.145 (− 0.084, 0.379)	0.033 (− 0.176, 0.243)	0.166 (− 0.066, 0.4)	0.244 (0.036, 0.457)	0.086 (− 0.465, 0.633)	0.203 (− 0.362, 0.737)
Brexpiprazole 1 mg	0.23 (− 0.014, 0.474)	0.073 (− 0.048, 0.196)	0.073 (− 0.048, 0.195)	− 0.04 (− 0.116, 0.036)	0.093 (− 0.037, 0.223)	0.171 (0.096, 0.246)	0.012 (− 0.5, 0.521)	0.127 (− 0.403, 0.637)

Table 1 (continued)

	Caraprizine 0.1–0.3 mg/d	Caraprizine 1.5 mg/d	Caraprizin 3 mg/d	Olanzapine 6–12 mg + Fluoxetine 25–50 mg combination/d	Quetiapine 150–300 mg/d	Olanzapine 6–12 mg/d	Ziprasidone 160 mg/d	Ziprasidon 80 mg/d
Brexpiprazole 2–3 mg	0.297 (0.039, 0.551)	0.137 (– 0.009, 0.285)	0.138 (– 0.009, 0.284)	0.024 (– 0.088, 0.136)	0.158 (0.044, 0.269)	0.235 (0.124, 0.347)	0.077 (– 0.444, 0.591)	0.193 (– 0.345, 0.709)
Brexpiprazole 2 mg	0.199 (– 0.057, 0.456)	0.041 (– 0.103, 0.19)	0.041 (– 0.105, 0.187)	– 0.072 (– 0.184, 0.04)	0.062 (– 0.092, 0.211)	0.139 (0.027, 0.251)	– 0.021 (– 0.536, 0.501)	0.096 (– 0.435, 0.612)
Brexpiprazole 3 mg	0.182 (– 0.063, 0.424)	0.023 (– 0.099, 0.148)	0.023 (– 0.1, 0.148)	– 0.09 (– 0.17, – 0.012)	0.044 (– 0.086, 0.176)	0.122 (0.042, 0.2)	– 0.037 (– 0.547, 0.474)	0.079 (– 0.453, 0.587)
Caraprizine 1–2 mg	0.045 (– 0.197, 0.283)	– 0.113 (– 0.282, 0.052)	– 0.114 (– 0.279, 0.05)	– 0.227 (– 0.363, – 0.093)	– 0.093 (– 0.264, 0.075)	– 0.016 (– 0.151, 0.119)	– 0.173 (– 0.702, 0.351)	– 0.057 (– 0.608, 0.466)
Caraprizine 2–4.5 mg	0.056 (– 0.205, 0.314)	– 0.102 (– 0.278, 0.075)	– 0.103 (– 0.276, 0.073)	– 0.216 (– 0.364, – 0.068)	– 0.083 (– 0.261, 0.099)	– 0.005 (– 0.151, 0.142)	– 0.162 (– 0.696, 0.363)	– 0.047 (– 0.594, 0.482)
Caraprizine 0.1–0.3 mg	0	– 0.159 (– 0.415, 0.102)	– 0.158 (– 0.415, 0.101)	– 0.272 (– 0.509, – 0.03)	– 0.137 (– 0.402, 0.124)	– 0.061 (– 0.298, 0.179)	– 0.217 (– 0.774, 0.343)	– 0.104 (– 0.68, 0.457)
Caraprizine 1.5 mg	0.159 (– 0.102, 0.415)	0	0 (– 0.109, 0.106)	– 0.114 (– 0.229, 0.001)	0.02 (– 0.133, 0.177)	0.098 (– 0.018, 0.214)	– 0.06 (– 0.58, 0.462)	0.055 (– 0.484, 0.569)
Caraprizine 3 mg	0.158 (– 0.101, 0.415)	0 (– 0.106, 0.109)	0	– 0.113 (– 0.228, 0.003)	0.02 (– 0.132, 0.178)	0.098 (– 0.016, 0.214)	– 0.061 (– 0.581, 0.46)	0.055 (– 0.483, 0.572)
Olanzapine 6–12 mg + Fluoxetine 25–50 mg combination	0.272 (0.03, 0.509)	0.114 (– 0.001, 0.229)	0.113 (– 0.003, 0.228)	0	0.133 (0.012, 0.257)	0.212 (0.167, 0.256)	0.052 (– 0.455, 0.559)	0.169 (– 0.367, 0.674)
Quetiapine 150–300 mg	0.137 (– 0.124, 0.402)	– 0.02 (– 0.177, 0.133)	– 0.02 (– 0.178, 0.132)	– 0.133 (– 0.257, – 0.012)	0	0.078 (– 0.046, 0.199)	– 0.079 (– 0.604, 0.437)	0.034 (– 0.506, 0.549)
Olanzapine 6–12 mg	0.061 (– 0.179, 0.298)	– 0.098 (– 0.214, 0.018)	– 0.098 (– 0.214, 0.016)	– 0.212 (– 0.256, – 0.167)	– 0.078 (– 0.199, 0.046)	0	– 0.159 (– 0.669, 0.353)	– 0.043 (– 0.577, 0.462)
Ziprasidon 160 mg/d	0.217 (– 0.343, 0.774)	0.06 (– 0.462, 0.58)	0.061 (– 0.46, 0.581)	– 0.052 (– 0.559, 0.455)	0.079 (– 0.437, 0.604)	0.159 (– 0.353, 0.669)	0	0.117 (– 0.418, 0.631)
Ziprasidone 80 mg/d	0.104 (– 0.457, 0.68)	– 0.055 (– 0.569, 0.484)	– 0.055 (– 0.572, 0.483)	– 0.169 (– 0.674, 0.367)	– 0.034 (– 0.549, 0.506)	0.043 (– 0.462, 0.577)	– 0.117 (– 0.631, 0.418)	0

Exclusion criteria

(1) Studies that evaluated only bipolar patients or TRD with psychotic features; patients with post-partum depression or prenatal depression or co-morbided with serious medical illnesses.
(2) Reviews, letters, case series, or conference proceedings.
(3) Non-interventional or non-randomized or single arm studies.
(4) Duplicate cohort.
(5) Non-English articles.

Study screening and quality assessment and data extraction

Two investigators (Binru Bai, Yuwei Li) independently searched and screened eligible studies by reading title, abstract, or the full text if needed, and assessed the qualities of enrolled studies by Review Manager 5.3 deploying the Cochrane Collaboration's Risk Interventions Risk of Bias Tool (2nd edition, ROB2) [20]. The following data were collected: Author name, nation, year, average age of patients, diagnosis, number of patients in each group, gender, MADRS, CGI-S, MARDS response rate, MARDS remission rate, etc. Any discrepancy was arbitrated by a senior investigator (Xi Chen).

Statistical analysis

STATA 18.0 MP was used to generate Napierian logarithm hazard ratio (lnHR) and standard error of lnHR (selnHR) for dichotomous variants and standard mean difference (SMD) and standard error (SE) for constant variables. Subsequently these two data were input into R 4.3.2 by ″gemtc″ package to conduct Bayesian network meta-analysis as well as Bayesian network meta-regression adjusting follow-up period to generate surface under the cumulative ranking curve (SUCRA) and matrix as well as trace plots, density plots, and Brooks-Rubin-Gelman diagnostic plots. A higher SUCRA indicates a higher probability of becoming a better regimen, however, whether the effect size of any pairwise comparison with corresponding SUCRAs of all the regimens reached significance was judged from matrix. Markov chain Monte Carlo (MCMC) was employed to obtain posterior distributions. We set the iteration times to 300,000 of 4 each chain, with 20,000 burn-in iterations and a thinning interval of 10 for each outcome. Statistical heterogeneity was tested using I^2 and p value. A fixed effect model was applied if there was no heterogeneity ($I^2 < 50\%$ and $P > 0.01$), otherwise the random effect model would be applied. If $I^2 > 75\%$, then Galbraith plots would be drawn to exclude studies outside the outlines to annihilate heterogeneity. To reinforce the results, overall and loops inconsistency test and consistency tests were carried out in each outcome. Statistical significance (α) was set at 0.05.

After adjusting follow-up period by Bayesian network regression analysis, the time-effect relationship curves were generated. GetData 2.26 was implemented to capture the"time window"(namely the period from being active to inactive, statistically the period from being statistically significant to non-significant of regimens compared with ADT) from the curves.

Endpoints

primary endpoint: MADRS score.

secondary endpoint: MADRS response rate.

tertiary endpoints: CGI-S score and MADRS remission rate.

Results

Characteristics of the included studies and risk of bias

Eventually, a total of 23 studies comprising 10679 patients with 24 regimens were enrolled (Fig. 1). The 24 regimens were listed in supplementary materials Table 2.

The mean ages across the study ranged from 38.1 to 46.6, the proportions of female ranged from 35.5% to 78.0%. The follow up duration ranged from 6 weeks to 16 weeks. The diagnosis of TRD was based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) or DSM- 5 (see supplement materials Table 2). Regarding the quality of enrolled studies, most studies were with moderate-to-high quality (see supplement materials Fig. 1).

Primary endpoint

There were 16 regimens available for assessing this endpoint, the most administrated agent was ADT ($n = 2511$), followed by brexpiprazole 2 mg/d ($n = 611$) and brexpiprazole 1 mg/d ($n = 473$). (Fig. 2).

In the raw data-analysis, aripiprazole 3–12 mg/d (SMD = − 0.28, 95%CI: − 0.487 to − 0.078, brexpiprazole 1 mg/d (SMD = − 0.208, 95%CI: − 0.267 to − 0.148), brexpiprazole 2–3 mg/d (SMD = − 0.272, 95%CI: − 0.374 to − 0.172), brexpiprazole 2 mg/d (SMD = − 0.175, 95%CI: − 0.278 to − 0.075), brexpiprazole 3 mg/d (SMD = − 0.158, 95%CI: − 0.222 to − 0.095), cariprazine 1.5 mg/d (SMD = − 0.135, 95%CI: − 0.24 to − 0.028), cariprazine 3 mg/d (SMD = − 0.135, 95%CI: − 0.242 to − 0.029), olanzapine 6–12 mg/d and fluoxetine 25–50 mg/d combination (SMD = − 0.248, 95%CI: − 0.295 to − 0.2) and quetiapine XR 150–300 mg/d (SMD = − 0.114, 95%CI: − 0.229 to − 0.01) were conspicuously effective compared with ADT. However, brexpiprazole 3 mg/d (SMD = − 0.158, 95%CI: − 0.222 to − 0.095) and quetiapine

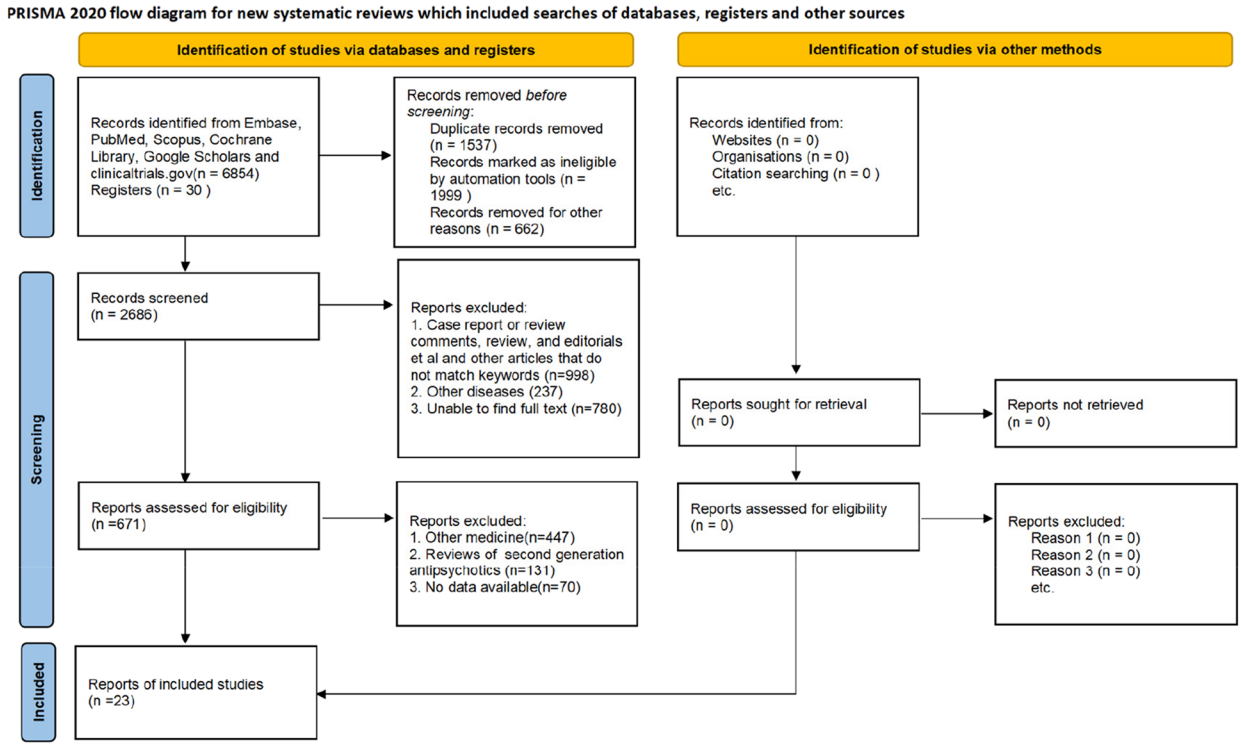

Fig. 1 Flow chart of the screening procedure

XR 150–300 mg/d (SMD = − 0.114, 95%CI: − 0.229 to − 0.01) were evidently inferior to the rests (Table 1).

After adjusting follow-up period, the results basically resembled the former (Table 2). However, quetiapine 150–300 mg/d (SMD = − 0.10 95%CI: − 0.212 to 0.014) failed to show priority over ADT (Table 2).

With regard to the"time window", the significance of brexpiprazole 3 mg/d lasted merely till 7.22 weeks. Although comparable with ADT, cariprazine 1–2 mg/d (2.97 weeks) (Fig. 3-(1)), bexpiprazole 3 mg/d (7.22 weeks) (Fig. 3-(2)), cariprazine 3 mg/d (7.16 weeks) (Fig. 3-(3)), quetiapine 150–300 mg/d (3.89 weeks) (Fig. 3-(4)), olanzapine 6–12 mg/d (4.11 weeks) (Fig. 3-(5)), and cariprazine 2–4.5 mg/d (2.81 weeks) (Fig. 3-(6)) were significantly effective within certain period, namely those showed"time window". Exclusively, aripiprazole 3–12 mg/d showed no"time window"effect, namely its significance compared with ADT lasted from beginning to the longest period (8 weeks) in our study. The X-axis represents follow-up period, the Y-axis represents standard mean difference (effect size, ES) of ADT versus SGAs, in each figure, the black solid line represents mean ESs, the upper dash line represents the 95% upper limit, the lower dash line represents the 95% lower limit. The red solid lines are auxiliary lines determining the precise timing of significance of regimens compared with ADT (namely"time window") (Fig. 3).

Secondary efficacy endpoint

There were 16 regimens available for assessing this endpoint, the most administrated agent was ADT (n = 2553), followed by cariprazine 1.5–4.5 mg/d (n = 540) and brexpiprazole 1 mg/d (n = 459). (Fig. 4).

In the raw data-analysis, aripiprazole 2–20 mg/d (HR = 2.735, 95%CI: 2.064 to 3.64), brexpiprazole 1 mg/d (HR = 1.635, 95%CI:1.244 to 2.148), brexpiprazole 2 mg/d (HR = 1.434, 95%CI: 1.117 to 1.842), brexpiprazole 3 mg/d (HR = 1.752, 95%CI:1.176 to 2.617), cariprazine 1–2 mg/d (HR = 1.522, 95%CI: 1.173 to 1.993), cariprazine 1.5–4.5 mg/d (HR = 1.548, 95%CI: 1.233 to 1.939), rispridone 0.5–3 mg/d (HR = 2.814, 95%CI: 1.119 to 7.09) and rispridone 1–2 mg/d (HR = 2.207, 95%CI: 1.43 to 3.373) were conspicuously effective compared with ADT (Table 3). However, brexpiprazole 3 mg/d (HR = 1.752, 95%CI:1.176 to 2.617), rispridone 0.5–3 mg/d (HR = 2.814, 95%CI: 1.119 to 7.09) and rispridone 1–2 mg/d (HR = 2.207, 95%CI: 1.43 to 3.373) were evidently

superior to all others. The rest 5 regimens were comparable in terms of treating TRD. (Table 3).

After adjusting follow-up time, except for rispridone 0.5–3 mg/d, these effective regimens were equivalent in terms of effect size resembled the former (Table 4). Although comparable with ADT, brexpiprazole 2 mg/d (2.45–7.84 weeks) (Fig. 5-(1)), cariprazine1 - 2 mg/d (2.87 weeks) (Fig. 5-(2)), cariprazine 1.5–4.5 mg/d (2.48 weeks) (Fig. 5-(3)), rispridone 0.5–3 mg/d (5.24 weeks) (Fig. 5-(4)) were significantly effective within certain period. The X-axis represents follow-up period, the Y-axis represents standard mean difference (effect size, ES) of ADT versus SGAs, in each figure, the black solid line represents mean ESs, the upper dash line represents the 95% upper limit, the lower dash line represents the 95% lower limit. The red solid lines are auxiliary lines determining the precise timing of significance of regimens compared with ADT (namely"time window") (Fig. 5).

Tertiary endpoint

CGI-S

There were 23 regimens available for assessing this endpoint, the most administrated agent was ADT ($n = 3407$), followed by brexpiprazole 1 mg/d (n = 684) and brexpiprazole 2 mg/d (n = 611) (See supplementary materials Fig. 7).

In the raw data-analysis, aripiprazole 2–20 mg/d (SMD = − 0.335, 95%CI: − 0.462 to − 0.21), aripiprazole 3 mg/d (SMD = − 0.216, 95%CI: − 0.384 to − 0.045), brexpiprazole 1 mg/d (SMD = − 0.182, 95%CI:− 0.238 to − 0.127), brexpiprazole 2 mg/d (SMD = − 0.238, 95%CI:− 0.342 to − 0.138), brexpiprazole 3 mg/d (SMD = − 0.153, 95%CI: − 0.213 to − 0.094), cariprazine 3 mg/d (SMD = − 0.126, 95%CI: − 0.233 to − 0.019), rispridone 0.5–3 mg/d (SMD = − 0.438, 95%CI: − 0.862 to − 0.015) and olanzapine 6–12 mg/d and fluoxetine 25–50 mg/d combination (SMD = − 0.317, 95%CI: − 0.487 to − 0.148) were conspicuously effective compared with ADT. However, cariprazine 3 mg/d (SMD = − 0.126, 95%CI: − 0.233 to − 0.019) was evidently inferior to all others (See supplementary materials Table 3).

After adjusting follow-up time, the results basically resembled the former. But rispridone 0.5–3 mg/d was no longer significantly different compared with ADT. Cariprazine 3 mg/d was inferior to all others which were conspicuously effective compared with ADT. The respectively treatment"time window"of were cariprazine 3 mg/d and rispridone 0.5–3 mg/d not significantly after about 7.42 weeks and 5.45 weeks(See supplementary materials Table 4 and Fig. 8).

MADRS remission rate

There were 17 regimens available for assessing this endpoint, the most administrated agent was ADT (n = 2553), followed by brexpiprazole 2 mg/d (n = 611) and cariprazine 1.5–4.5 mg/d (n = 480) (See supplementary materials Fig. 11).

In the raw data-analysis, aripiprazole 2–20 mg/d (HR = 2.556, 95%CI: 2.016 to 3.242), brexpiprazole 3 mg/d (HR = 1.563, 95%CI:1.04 to 2.378), cariprazine 3 mg/d (HR = 1.477, 95%CI: 1.042 to 2.097), rispridone 0.5–2 mg/d (HR = 2.611, 95%CI:1.438 to 4.728), rispridone 0.5–3 mg/d (HR = 3.326, 95%CI:1.618 to 6.749) were conspicuously effective compared with ADT (See supplementary materials Table 5).

After adjusting follow-up time, the results basically resembled the former. There was no treatment"time window"for regiments in this group. (See supplementary materials Table 6).

Heterogeneity and inconsistency and convergency

There was no prominent heterogeneity ($I^2 < 50\%$) in the direct comparisons on each endpoint.

The I^2 of overall and loops inconsistency was less than 50% and $p > 0.01$, indicating no overall inconsistency nor loops inconsistency between direct and indirect comparisons.

The trace plots and density plots and Brooks-Gelman-Rubin diagnostic plots showed good convergency of the model in both Bayesian network meta-analysis and Bayesian network meta-regression, collectively (See supplementary materials).

Discussion

To the best of our knowledge, this is the first Bayesian network meta-regression analysis investigating SGAs augmentation to anti-depressants in the treatment of TRD adjusting follow-up period.

Interpretation of our results

This NMR of 14 agents showed that SGAs, including aripiprazole, brexpiprazole, cariprazine, olanzapine, olanzapine-fluoxetine combination (based on ADT), quetiapine, and risperidone with corresponding dosages, etc., could be employed as adjunctive treatments for TRD.

Our findings not only justified dispute and incongruity regarding the efficacy of SGA augmentative treatment confronting TRD from previous literature, but also provide advanced and unprecedented data in terms of"time window", deepening clinical understanding of medication algorithm (including sequential therapy) in treating TRD, paving the way for further formulation or update of related guidelines [13, 14, 21–24].

Table 2 Matrix of pairwise comparisons on MADRS score for second-generation antipsychotics to augment the efficacy in treating treatment-resistant depression after adjustment (shown as standard mean difference and 95% confidence intervals)

	ADT	**Aripiprazole 3–12 mg/d**	**Brexpiprazole 1 mg/d**	**Brexpiprazole 2–3 mg/d**	**Brexpiprazole 2 mg/d**	**Brexpiprazole 3 mg/d**	**Caraprizine 1–2 mg/d**	**Caraprizine 2–4.5 mg/d**
ADT	0	− 0.313 (− 0.516, − 0.11)	− 0.196 (− 0.256, − 0.138)	− 0.255 (− 0.357, − 0.155)	− 0.208 (− 0.308, − 0.11)	− 0.138 (− 0.202, − 0.074)	− 0.1 (− 0.231, 0.033)	− 0.111 (− 0.256, 0.036)
Aripiprazole 3–12 mg/d	0.313 (0.11, 0.516)	0	0.117 (− 0.093, 0.327)	0.058 (− 0.168, 0.287)	0.105 (− 0.12, 0.328)	0.174 (− 0.037, 0.387)	0.213 (− 0.026, 0.444)	0.203 (− 0.045, 0.445)
Brexpiprazole 1 mg	0.196 (0.138, 0.256)	− 0.117 (− 0.327, 0.093)	0	− 0.059 (− 0.177, 0.057)	− 0.012 (− 0.121, 0.095)	0.058 (− 0.005, 0.121)	0.096 (− 0.05, 0.241)	0.086 (− 0.074, 0.245)
Brexpiprazole 2–3 mg	0.255 (0.155, 0.357)	− 0.058 (− 0.287, 0.168)	0.059 (− 0.057, 0.177)	0	0.046 (− 0.098, 0.19)	0.116 (− 0.003, 0.236)	0.155 (− 0.015, 0.325)	0.145 (− 0.035, 0.322)
Brexpiprazole 2 mg	0.208 (0.11, 0.308)	− 0.105 (− 0.328, 0.12)	0.012 (− 0.095, 0.121)	− 0.046 (− 0.19, 0.098)	0	0.07 (− 0.045, 0.185)	0.107 (− 0.055, 0.268)	0.097 (− 0.075, 0.271)
Brexpiprazole 3 mg	0.138 (0.074, 0.202)	− 0.174 (− 0.387, 0.037)	− 0.058 (− 0.121, 0.005)	− 0.116 (− 0.236, 0.003)	− 0.07 (− 0.185, 0.045)	0	0.038 (− 0.115, 0.186)	0.028 (− 0.135, 0.189)
Caraprizine 1–2 mg	0.1 (− 0.033, 0.231)	− 0.213 (− 0.444, 0.026)	− 0.096 (− 0.241, 0.05)	− 0.155 (− 0.325, 0.015)	− 0.107 (− 0.268, 0.055)	− 0.038 (− 0.186, 0.115)	0	− 0.01 (− 0.15, 0.128)
Caraprizine 2–4.5 mg	0.111 (− 0.036, 0.256)	− 0.203 (− 0.445, 0.045)	− 0.086 (− 0.245, 0.074)	− 0.145 (− 0.322, 0.035)	− 0.097 (− 0.271, 0.075)	− 0.028 (− 0.189, 0.135)	0.01 (− 0.128, 0.15)	0
Caraprizine 0.1–0.3 mg	0.057 (− 0.185, 0.291)	− 0.256 (− 0.561, 0.05)	− 0.14 (− 0.382, 0.104)	− 0.199 (− 0.455, 0.06)	− 0.151 (− 0.411, 0.102)	− 0.081 (− 0.331, 0.165)	− 0.045 (− 0.28, 0.189)	− 0.054 (− 0.313, 0.203)
Caraprizine 1.5 mg	0.169 (0.06, 0.274)	− 0.144 (− 0.371, 0.081)	− 0.028 (− 0.151, 0.096)	− 0.086 (− 0.238, 0.062)	− 0.04 (− 0.183, 0.103)	0.03 (− 0.095, 0.156)	0.067 (− 0.097, 0.234)	0.057 (− 0.121, 0.234)
Caraprizine 3 mg	0.168 (0.064, 0.273)	− 0.146 (− 0.373, 0.083)	− 0.029 (− 0.149, 0.093)	− 0.087 (− 0.234, 0.06)	− 0.041 (− 0.181, 0.103)	0.03 (− 0.093, 0.153)	0.068 (− 0.098, 0.231)	0.058 (− 0.119, 0.233)
Olanzapine 6–12 mg + Fluoxetine 25–50 mg combination	0.241 (0.191, 0.289)	− 0.072 (− 0.282, 0.135)	0.045 (− 0.032, 0.12)	− 0.014 (− 0.126, 0.096)	0.032 (− 0.079, 0.143)	0.103 (0.023, 0.181)	0.14 (− 0.005, 0.283)	0.13 (− 0.025, 0.285)
Quetiapine 150–300 mg	0.1 (− 0.014, 0.212)	− 0.214 (− 0.448, 0.019)	− 0.096 (− 0.224, 0.031)	− 0.155 (− 0.268, − 0.042)	− 0.109 (− 0.261, 0.043)	− 0.039 (− 0.167, 0.091)	− 0.001 (− 0.177, 0.176)	− 0.011 (− 0.199, 0.179)
Olanzapine 6–12 mg	0.029 (− 0.018, 0.077)	− 0.283 (− 0.493, − 0.077)	− 0.167 (− 0.24, − 0.09)	− 0.225 (− 0.336, − 0.113)	− 0.179 (− 0.289, − 0.069)	− 0.109 (− 0.188, − 0.029)	− 0.071 (− 0.216, 0.072)	− 0.081 (− 0.237, 0.074)
Ziprasidon 160 mg/d	0.263 (− 0.225, 0.755)	− 0.052 (− 0.577, 0.479)	0.065 (− 0.424, 0.56)	0.005 (− 0.491, 0.509)	0.053 (− 0.441, 0.556)	0.125 (− 0.367, 0.62)	0.161 (− 0.342, 0.67)	0.151 (− 0.363, 0.657)
Ziprasidone 80 mg/d	0.148 (− 0.343, 0.624)	− 0.162 (− 0.703, 0.357)	− 0.048 (− 0.542, 0.434)	− 0.107 (− 0.612, 0.385)	− 0.059 (− 0.555, 0.428)	0.011 (− 0.492, 0.491)	0.048 (− 0.464, 0.543)	0.038 (− 0.473, 0.54)
	Caraprizine 0.1–0.3 mg/d	**Caraprizine 1.5 mg/d**	**Caraprizin 3 mg/d**	**Olanzapine 6–12 mg + Fluoxetine 25–50 mg combination/d**	**Quetiapine 150–300 mg/d**	**Olanzapine 6–12 mg/d**	**Ziprasidone 160 mg/d**	**Ziprasidon 80 mg/d**
ADT	− 0.057 (− 0.291, 0.185)	− 0.169 (− 0.274, − 0.06)	− 0.168 (− 0.273, − 0.064)	− 0.241 (− 0.289, − 0.191)	− 0.1 (− 0.212, 0.014)	− 0.029 (− 0.077, 0.018)	− 0.263 (− 0.755, 0.225)	− 0.148 (− 0.624, 0.343)
Aripiprazole 3–12 mg/d	0.256 (− 0.05, 0.561)	0.144 (− 0.081, 0.371)	0.146 (− 0.083, 0.373)	0.072 (− 0.135, 0.282)	0.214 (− 0.019, 0.448)	0.283 (0.077, 0.493)	0.052 (− 0.479, 0.577)	0.162 (− 0.357, 0.703)

Table 2 (continued)

	Caraprizine 0.1–0.3 mg/d	Caraprizine 1.5 mg/d	Caraprizin 3 mg/d	Olanzapine 6–12 mg + Fluoxetine 25–50 mg combination/d	Quetiapine 150–300 mg/d	Olanzapine 6–12 mg/d	Ziprasidone 160 mg/d	Ziprasidon 80 mg/d
Brexpiprazole 1 mg	0.14 (– 0.104, 0.382)	0.028 (– 0.096, 0.151)	0.029 (– 0.093, 0.149)	– 0.045 (– 0.12, 0.032)	0.096 (– 0.031, 0.224)	0.167 (0.09, 0.24)	– 0.065 (– 0.56, 0.424)	0.048 (– 0.434, 0.542)
Brexpiprazole 2–3 mg	0.199 (– 0.06, 0.455)	0.086 (– 0.062, 0.238)	0.087 (– 0.06, 0.234)	0.014 (– 0.096, 0.126)	0.155 (0.042, 0.268)	0.225 (0.113, 0.336)	– 0.005 (– 0.509, 0.491)	0.107 (– 0.385, 0.612)
Brexpiprazole 2 mg	0.151 (– 0.102, 0.411)	0.04 (– 0.103, 0.183)	0.041 (– 0.103, 0.181)	– 0.032 (– 0.143, 0.079)	0.109 (– 0.043, 0.261)	0.179 (0.069, 0.289)	– 0.053 (– 0.556, 0.441)	0.059 (– 0.428, 0.555)
Brexpiprazole 3 mg	0.081 (– 0.165, 0.331)	– 0.03 (– 0.156, 0.095)	– 0.03 (– 0.153, 0.093)	– 0.103 (– 0.181, – 0.023)	0.039 (– 0.091, 0.167)	0.109 (0.029, 0.188)	– 0.125 (– 0.62, 0.367)	– 0.011 (– 0.491, 0.492)
Caraprizine 1–2 mg	0.045 (– 0.189, 0.28)	– 0.067 (– 0.234, 0.097)	– 0.068 (– 0.231, 0.098)	– 0.14 (– 0.283, 0.005)	0.001 (– 0.176, 0.177)	0.071 (– 0.072, 0.216)	– 0.161 (– 0.67, 0.342)	– 0.048 (– 0.543, 0.464)
Caraprizine 2–4.5 mg	0.054 (– 0.203, 0.313)	– 0.057 (– 0.234, 0.121)	– 0.058 (– 0.233, 0.119)	– 0.13 (– 0.285, 0.025)	0.011 (– 0.179, 0.199)	0.081 (– 0.074, 0.237)	– 0.151 (– 0.657, 0.363)	– 0.038 (– 0.54, 0.473)
Caraprizine 0.1–0.3 mg	0	– 0.111 (– 0.365, 0.146)	– 0.112 (– 0.371, 0.147)	– 0.183 (– 0.429, 0.055)	– 0.042 (– 0.308, 0.222)	0.028 (– 0.218, 0.268)	– 0.205 (– 0.744, 0.336)	– 0.094 (– 0.627, 0.449)
Caraprizine 1.5 mg	0.111 (– 0.146, 0.365)	0	0 (– 0.106, 0.104)	– 0.072 (– 0.191, 0.043)	0.068 (– 0.087, 0.226)	0.139 (0.021, 0.253)	– 0.094 (– 0.591, 0.413)	0.02 (– 0.468, 0.53)
Caraprizine 3 mg	0.112 (– 0.147, 0.371)	0 (– 0.104, 0.106)	0	– 0.073 (– 0.187, 0.043)	0.068 (– 0.084, 0.225)	0.139 (0.023, 0.253)	– 0.094 (– 0.597, 0.405)	0.018 (– 0.467, 0.527)
Olanzapine 6–12 mg + Fluoxetine 25–50 mg combination	0.183 (– 0.055, 0.429)	0.072 (– 0.043, 0.191)	0.073 (– 0.043, 0.187)	0	0.141 (0.019, 0.264)	0.211 (0.166, 0.256)	– 0.022 (– 0.517, 0.473)	0.091 (– 0.386, 0.587)
Quetiapine 150–300 mg	0.042 (– 0.222, 0.308)	– 0.068 (– 0.226, 0.087)	– 0.068 (– 0.225, 0.084)	– 0.141 (– 0.264, – 0.019)	0	0.071 (– 0.054, 0.191)	– 0.161 (– 0.666, 0.337)	– 0.05 (– 0.548, 0.466)
Olanzapine 6–12 mg	– 0.028 (– 0.268, 0.218)	– 0.139 (– 0.253, – 0.021)	– 0.139 (– 0.253, – 0.023)	– 0.211 (– 0.256, – 0.166)	– 0.071 (– 0.191, 0.054)	0	– 0.234 (– 0.729, 0.261)	– 0.12 (– 0.597, 0.376)
Ziprasidon 160 mg/d	0.205 (– 0.336, 0.744)	0.094 (– 0.413, 0.591)	0.094 (– 0.405, 0.597)	0.022 (– 0.473, 0.517)	0.161 (– 0.337, 0.666)	0.234 (– 0.261, 0.729)	0	0.117 (– 0.403, 0.624)
Ziprasidone 80 mg/d	0.094 (– 0.449, 0.627)	– 0.02 (– 0.53, 0.468)	– 0.018 (– 0.527, 0.467)	– 0.091 (– 0.587, 0.386)	0.05 (– 0.466, 0.548)	0.12 (– 0.376, 0.597)	– 0.117 (– 0.624, 0.403)	0

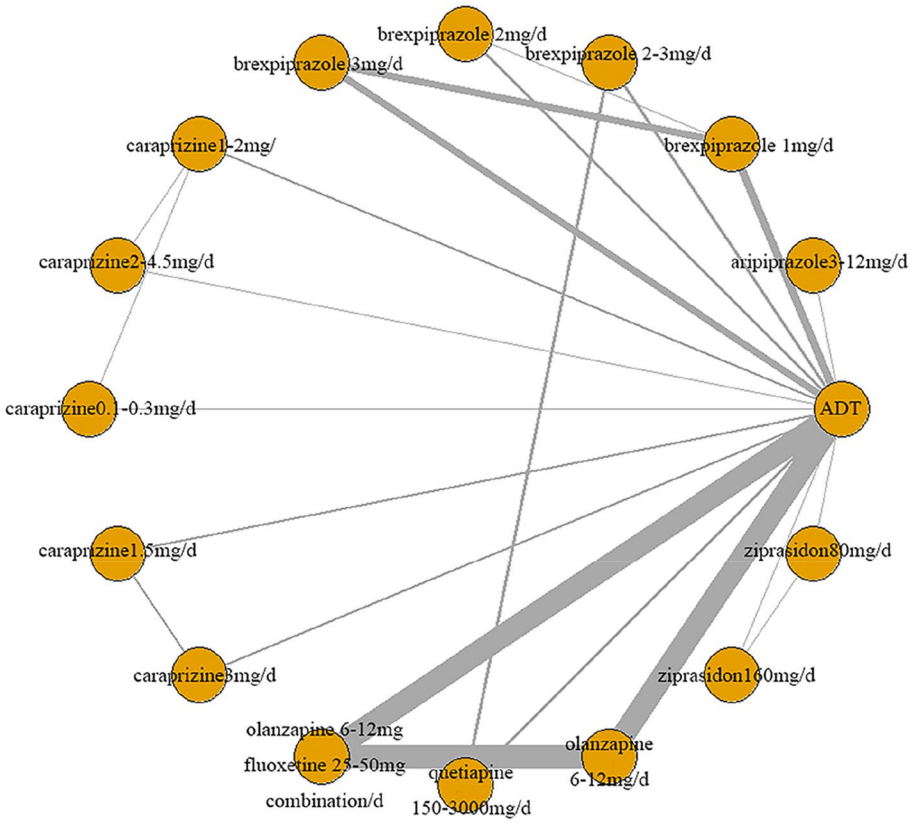

Fig. 2 Network graph of MADRS pairwise comparisons of regimens for second-generation antipsychotics (SGA) augmentation on treatment-resistant depression

Our result that aripiprazole was effective in the augmentative treatment of TRD was consistent with previous studies [25]. Most imperatively, our results supported pharmacologically augmented recommendations for aripiprazole and brexpiprazole from"2023 Update on Clinical Guidelines for Management of Major Depressive Disorder in Adults"drafted by CANMAT, which were listed as first-line agents to enhance oral antidepressant therapy [26].

According to our study, across all the endpoints, aripiprazole with fixed dose or flexible dose was long-term (namely no"time window"effect) effective in patients with TRD. In consistent to our results, a 6-week RCT showed a significant improvement in mean MADRS score with fixed-dose and flexible-dose aripiprazole compared with ADT in Japanese TRD patients [27].

A meta-analysis investigating anti-depression remedies in treating TRD showed that the response rate of aripiprazole was significantly higher than placebo [16]. Similarly, aripiprazole was regarded to be effective with doses ranged from 2 to 20 mg per day, rapid onset of effect and lasts long duration of maintenance (from initiation of medication to the longest follow-up period, namely 0–8 weeks) from our study.

Establishing clinical-pathological correlation

Both aripiprazole and brexpiprazole are dopamine receptor partial agonists, and brexpiprazole has less intrinsic agonist activity at D_2 receptor than aripiprazole [28]. Compared with aripiprazole, brexpiprazole has lower D_2 intrinsic activity, although the latter features a more potent serotonergic 5-$HT_{2\ A}$ antagonism [29], which means that more favorable tolerability and safety should be expected. However, in terms of improving MADRS score, our study showed no significant difference between brexpiprazole 3 mg/d and ADT after 7.22 weeks. In addition, a meta-analysis showed that brexpiprazole was most effective at doses up to about 2 mg/d, and then showed a downward trend at higher allowable doses up to 3 mg [30].This is similar to the results of Dean F Wong's study, which found that multiple doses of 2 mg/d are expected to result in D_2/D_3 receptor occupancies of around 80%, which is regarded as a clinically effective threshold [31]. D_2 partial agonism, which may theoretically account for different clinical activities depending on the dose [32, 33].

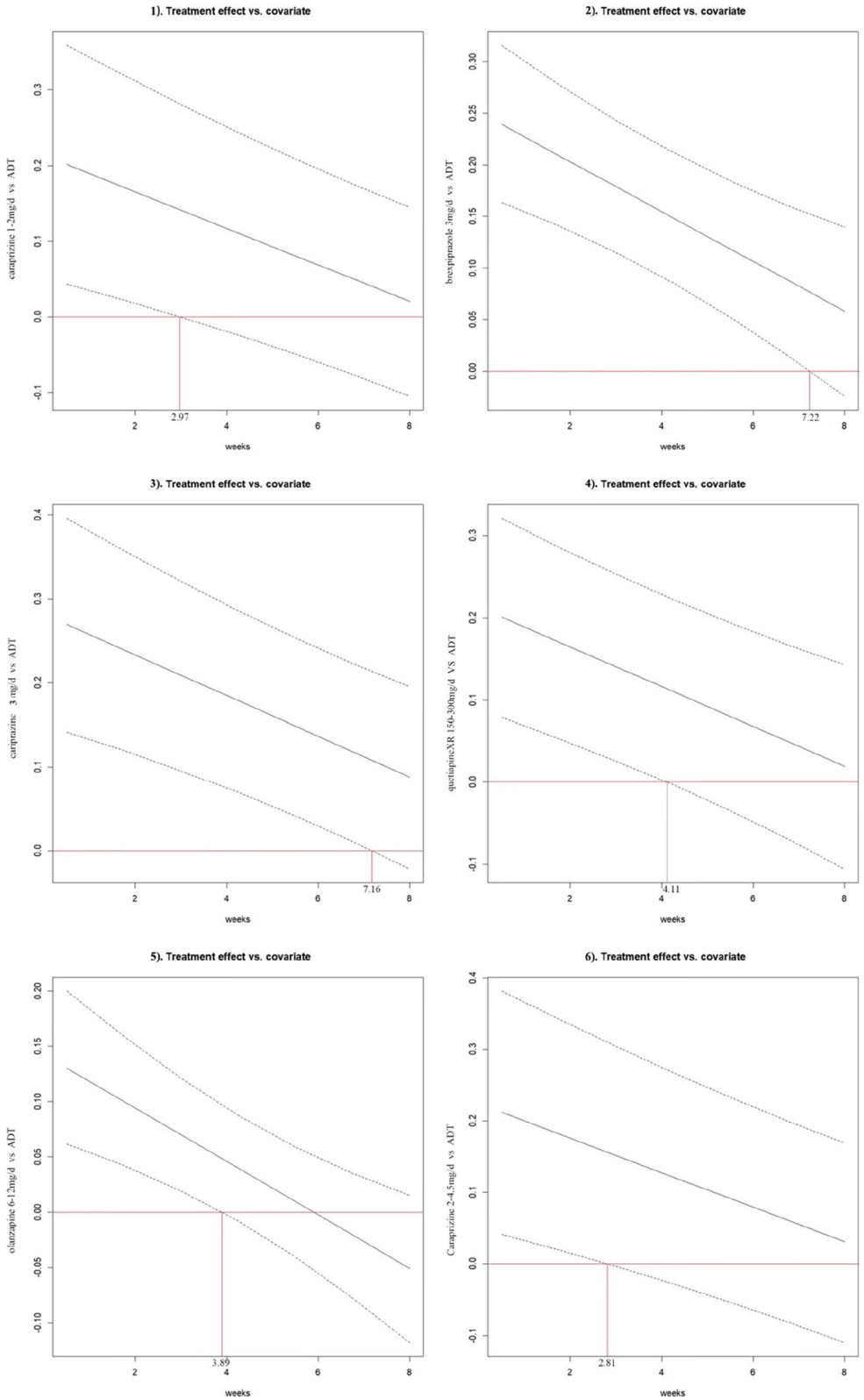

Fig. 3 Time-effect size curves of MADRS score

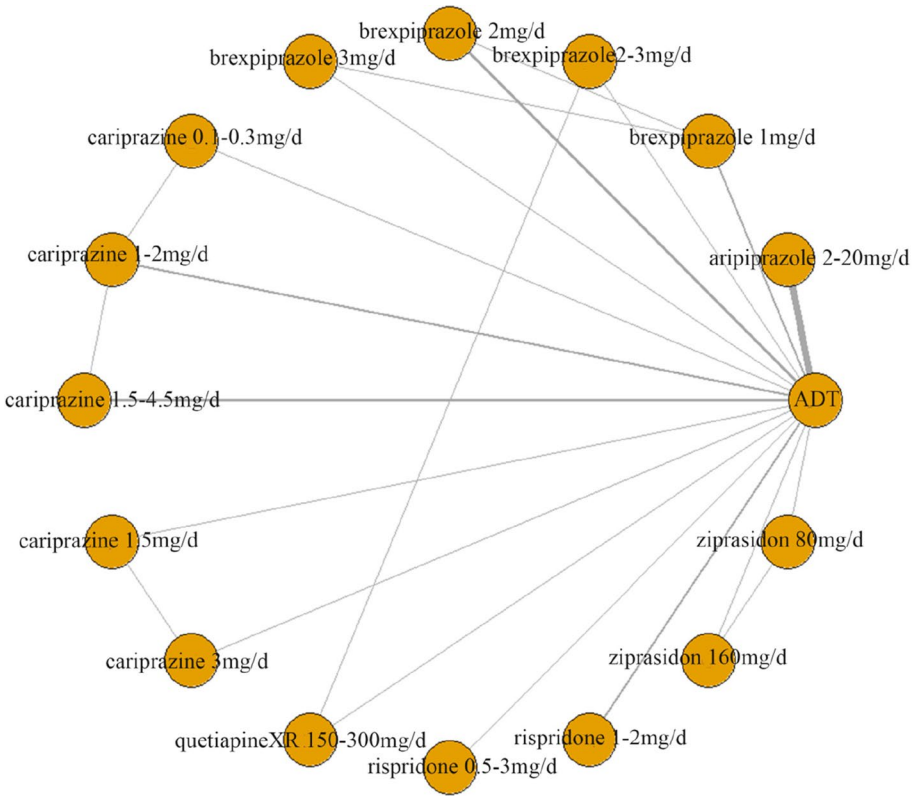

Fig. 4 Network graph of MADRS response rate pairwise comparisons of regimens for second-generation antipsychotics (SGA) augmentation on treatment-resistant depression

Cariprazine is a D_3-preferring dopamine D_2/D_3 receptor partial agonist, with a higher affinity for D_3 receptors [34]. Dopamine D_3 receptor blocking may have pro-cognitive and antidepressant effects [35, 36]. Cariprazine has been approved by the FDA for the treatment of schizophrenia and bipolar I disorder, and in recent years, more and more studies have focused on cariprazine adjuvant treatment of TRD. Studies have shown that cariprazine can significantly reduce MADRS scores compared to ADT [37–39].

However, the optimal effective dose of cariprazine is still under debating. For instance, a 6-week RCT showed that the mean reduction of MADRS total score from baseline was significantly greater with cariprazine 1.5 mg/d compared with ADT, but paradoxically, cariprazine 3.0 mg/d failed to show superiority [39].

On the contrary, another study showed that cariprazine 2–4.5 mg/d, compared with cariprazine 1–2 mg/d, showed superior efficacy on MADRS score, which was philosophical [37].

Our study showed that the average"time window"of cariprazine 3 mg/d in both MADRS score and CGI-S score endpoints was about 7.26 weeks, while the average"time window"of cariprazine 1–2 mg/d and cariprazine 2–4.5 mg/d in the aforementioned endpoints was about 2.88 weeks, which was paradoxical, either.

Consider the possible reasons, cariprazine has a fairly long half-life (2 to 4 days) [40], Whether it is more likely to fatigue the receptor and trigger drug resistance. The optimal effective threshold is not the highest dose, which may be due to personalized medication or genetic variation of CYP2D6. Patients with genetic variants of CYP2D6 may be slow or fast metabolizers of certain drugs [41]. More related studies are entailed to investigate this phenomenon in the future.

A meta-analysis investigating anti-depressants regimens in treating TRD showed that the efficacy of risperidone at 2nd, 4th, and 6th week was second merely to that of quetiapine augmentation (800 mg/day) [17]. Previous study has shown that, in terms of quality of life or functioning, risperidone was superior to ADT [42]. Those were consistent with our findings. In terms of response rates, regiments such as risperidone were superior to ADT after adjustment [43–45].

Table 3 Matrix of pairwise comparisons on MADRS response rate for second-generation antipsychotics to augment the efficacy in treating treatment-resistant depression (shown as hazard ratio and 95% confidence intervals)

	ADT	Aripiprazole 3–12 mg/d	Brexpiprazole 1 mg/d	Brexpiprazole 2–3 mg/d	Brexpiprazole 2 mg/d	Brexpiprazole 3 mg/d	Cariprazin 0.1–0.3 mg/d	Cariprazine 1–2 mg/d
ADT	1	2.735 (2.064, 3.64)	1.635 (1.244, 2.148)	1.608 (0.841, 3.041)	1.434 (1.117, 1.842)	1.752 (1.176, 2.617)	1.148 (0.682, 1.943)	1.522 (1.173, 1.993)
Aripiprazole 3–12 mg/d	0.366 (0.275, 0.485)	1	0.598 (0.403, 0.885)	0.588 (0.289, 1.183)	0.525 (0.358, 0.764)	0.64 (0.394, 1.042)	0.42 (0.232, 0.767)	0.558 (0.378, 0.819)
Brexpiprazole 1 mg/d	0.612 (0.466, 0.804)	1.671 (1.13, 2.478)	1	0.986 (0.484, 1.965)	0.878 (0.643, 1.19)	1.072 (0.73, 1.581)	0.704 (0.388, 1.267)	0.931 (0.637, 1.369)
Brexpiprazole 2–3 mg/d	0.622 (0.329, 1.189)	1.702 (0.845, 3.457)	1.014 (0.509, 2.067)	1	0.89 (0.451, 1.793)	1.088 (0.515, 2.334)	0.714 (0.313, 1.64)	0.946 (0.472, 1.914)
Brexpiprazole 2 mg/d	0.697 (0.543, 0.895)	1.906 (1.31, 2.79)	1.14 (0.84, 1.556)	1.123 (0.558, 2.216)	1	1.223 (0.786, 1.912)	0.801 (0.448, 1.436)	1.062 (0.738, 1.534)
Brexpiprazole 3 mg/d	0.571 (0.382, 0.85)	1.561 (0.96, 2.539)	0.933 (0.632, 1.369)	0.919 (0.429, 1.943)	0.818 (0.523, 1.273)	1	0.655 (0.339, 1.258)	0.869 (0.539, 1.403)
Cariprazin 0.1–0.3 mg/d	0.871 (0.515, 1.466)	2.382 (1.304, 4.307)	1.421 (0.789, 2.576)	1.401 (0.61, 3.199)	1.249 (0.697, 2.234)	1.528 (0.795, 2.95)	1	1.327 (0.787, 2.221)
Cariprazine 1–2 mg/d	0.657 (0.502, 0.853)	1.793 (1.221, 2.645)	1.074 (0.73, 1.569)	1.057 (0.522, 2.118)	0.941 (0.652, 1.355)	1.15 (0.713, 1.856)	0.753 (0.45, 1.271)	1
Cariprazine1.5–4.5 mg/d	0.646 (0.516, 0.811)	1.765 (1.235, 2.536)	1.056 (0.742, 1.506)	1.038 (0.525, 2.04)	0.926 (0.663, 1.299)	1.132 (0.719, 1.793)	0.742 (0.43, 1.294)	0.984 (0.744, 1.305)
Cariprazine 1.5 mg/d	0.803 (0.581, 1.114)	2.197 (1.428, 3.39)	1.313 (0.86, 2.011)	1.29 (0.624, 2.647)	1.15 (0.766, 1.736)	1.409 (0.839, 2.345)	0.922 (0.501, 1.704)	1.222 (0.806, 1.864)
Cariprazine 3 mg/d	0.735 (0.528, 1.017)	2.011 (1.298, 3.091)	1.201 (0.783, 1.841)	1.181 (0.57, 2.41)	1.054 (0.695, 1.584)	1.289 (0.766, 2.153)	0.844 (0.456, 1.557)	1.119 (0.738, 1.707)
QuetiapineXR150 - 300 mg/d	0.833 (0.405, 1.702)	2.275 (1.059, 4.963)	1.361 (0.629, 2.928)	1.339 (0.666, 2.681)	1.194 (0.558, 2.545)	1.462 (0.639, 3.327)	0.954 (0.395, 2.335)	1.267 (0.59, 2.724)
Rispridone 0.5–3 mg/d	0.355 (0.141, 0.893)	0.969 (0.372, 2.551)	0.581 (0.222, 1.522)	0.572 (0.186, 1.752)	0.51 (0.195, 1.323)	0.622 (0.227, 1.704)	0.408 (0.142, 1.182)	0.543 (0.207, 1.412)
Rispridone 1–2 mg/d	0.453 (0.296, 0.699)	1.238 (0.745, 2.086)	0.74 (0.449, 1.241)	0.729 (0.337, 1.562)	0.649 (0.398, 1.068)	0.792 (0.447, 1.438)	0.521 (0.264, 1.022)	0.691 (0.417, 1.148)
Ziprasidon 160 mg/d	0.2 (0.029, 1.388)	0.547 (0.075, 3.902)	0.326 (0.046, 2.326)	0.319 (0.043, 2.436)	0.285 (0.041, 2.037)	0.352 (0.048, 2.548)	0.229 (0.031, 1.691)	0.302 (0.043, 2.172)
Ziprasidon 80 mg/d	1.003 (0.123, 8.429)	2.741 (0.327, 23.533)	1.636 (0.197, 14.027)	1.615 (0.174, 14.644)	1.436 (0.173, 12.31)	1.766 (0.208, 15.388)	1.158 (0.133, 10.333)	1.528 (0.185, 13.019)

	Cariprazine1.5–4.5 mg/d	Cariprazine 1.5 mg/d	Cariprazine 3 mg/d	QuetiapineXR 150–300 mg/d	Rispridone0.5 - 3 mg/d	Rispridone1 - 2 mg/d	Ziprasidon160 mg/d	Ziprasidon80 mg/d
ADT	1.548 (1.233, 1.939)	1.245 (0.897, 1.722)	1.36 (0.984, 1.894)	1.2 (0.587, 2.466)	2.814 (1.119, 7.09)	2.207 (1.43, 3.373)	5.009 (0.72, 34.599)	0.997 (0.119, 8.139)
Aripiprazole 3–12 mg/d	0.567 (0.394, 0.81)	0.455 (0.295, 0.701)	0.497 (0.324, 0.771)	0.44 (0.201, 0.945)	1.032 (0.392, 2.685)	0.808 (0.479, 1.343)	1.827 (0.256, 13.272)	0.365 (0.042, 3.062)

Table 3 (continued)

	Cariprazine1.5–4.5 mg/d	Cariprazine 1.5 mg/d	Cariprazine 3 mg/d	QuetiapineXR 150–300 mg/d	Rispridone0.5 - 3 mg/d	Rispridone1 - 2 mg/d	Ziprasidon160 mg/d	Ziprasidon80 mg/d
Brexpiprazole 1 mg/d	0.947 (0.664, 1.347)	0.762 (0.497, 1.162)	0.833 (0.543, 1.278)	0.735 (0.341, 1.591)	1.721 (0.657, 4.511)	1.351 (0.806, 2.229)	3.067 (0.43, 21.667)	0.611 (0.071, 5.067)
Brexpiprazole 2–3 mg/d	0.963 (0.49, 1.906)	0.775 (0.378, 1.603)	0.847 (0.415, 1.756)	0.747 (0.373, 1.501)	1.748 (0.571, 5.391)	1.372 (0.64, 2.971)	3.139 (0.41, 23.304)	0.619 (0.068, 5.736)
Brexpiprazole 2 mg/d	1.08 (0.77, 1.509)	0.869 (0.576, 1.306)	0.949 (0.631, 1.439)	0.837 (0.393, 1.792)	1.961 (0.756, 5.126)	1.54 (0.936, 2.516)	3.508 (0.491, 24.609)	0.696 (0.081, 5.785)
Brexpiprazole 3 mg/d	0.884 (0.558, 1.392)	0.71 (0.427, 1.192)	0.776 (0.464, 1.306)	0.684 (0.301, 1.564)	1.607 (0.587, 4.412)	1.262 (0.695, 2.235)	2.844 (0.392, 20.62)	0.566 (0.065, 4.808)
Cariprazin 0.1–0.3 mg/d	1.348 (0.773, 2.327)	1.084 (0.587, 1.998)	1.184 (0.642, 2.191)	1.048 (0.428, 2.533)	2.452 (0.846, 7.054)	1.918 (0.979, 3.781)	4.366 (0.592, 32.205)	0.863 (0.097, 7.543)
Cariprazine 1–2 mg/d	1.016 (0.766, 1.343)	0.818 (0.536, 1.24)	0.894 (0.586, 1.355)	0.789 (0.367, 1.695)	1.843 (0.708, 4.827)	1.448 (0.871, 2.401)	3.306 (0.46, 23.155)	0.654 (0.077, 5.404)
Cariprazine1.5–4.5 mg/d	1	0.806 (0.541, 1.196)	0.879 (0.594, 1.319)	0.775 (0.367, 1.651)	1.813 (0.704, 4.685)	1.425 (0.876, 2.307)	3.238 (0.46, 22.664)	0.642 (0.076, 5.307)
Cariprazine 1.5 mg/d	1.241 (0.836, 1.848)	1	1.093 (0.79, 1.52)	0.963 (0.441, 2.14)	2.255 (0.853, 6.035)	1.771 (1.032, 3.031)	4.016 (0.566, 28.547)	0.799 (0.093, 6.753)
Cariprazine 3 mg/d	1.138 (0.758, 1.684)	0.915 (0.658, 1.266)	1	0.882 (0.402, 1.948)	2.068 (0.778, 5.495)	1.621 (0.943, 2.771)	3.701 (0.514, 26.14)	0.732 (0.085, 6.196)
QuetiapineXR150 - 300 mg/d	1.291 (0.606, 2.723)	1.039 (0.467, 2.269)	1.134 (0.513, 2.489)	1	2.326 (0.73, 7.614)	1.838 (0.794, 4.253)	4.218 (0.508, 31.585)	0.831 (0.087, 7.497)
Rispridone 0.5–3 mg/d	0.552 (0.213, 1.42)	0.443 (0.166, 1.173)	0.483 (0.182, 1.286)	0.43 (0.131, 1.369)	1	0.786 (0.284, 2.144)	1.767 (0.209, 15.118)	0.353 (0.035, 3.583)
Rispridone 1–2 mg/d	0.702 (0.433, 1.141)	0.565 (0.33, 0.969)	0.617 (0.361, 1.061)	0.544 (0.235, 1.259)	1.273 (0.466, 3.527)	1	2.27 (0.315, 16.214)	0.449 (0.052, 3.881)
Ziprasidon 160 mg/d	0.309 (0.044, 2.173)	0.249 (0.035, 1.766)	0.27 (0.038, 1.947)	0.237 (0.032, 1.969)	0.566 (0.066, 4.794)	0.441 (0.062, 3.179)	1	0.199 (0.028, 1.336)
Ziprasidon 80 mg/d	1.558 (0.188, 13.206)	1.251 (0.148, 10.786)	1.366 (0.161, 11.74)	1.203 (0.133, 11.553)	2.836 (0.279, 28.627)	2.227 (0.258, 19.347)	5.013 (0.749, 35.17)	1

Table 4 Matrix of pairwise comparisons on MADRS response rate for second-generation antipsychotics to augment the efficacy in treating treatment-resistant depression after adjustment (shown as hazard ratio and 95% confidence intervals)

	ADT	aripiprazole3 - 12 mg/d	brexpiprazole1 mg/d	brexpiprazole2 - 3 mg/d	brexpiprazole2 mg/d	brexpiprazole3 mg/d	cariprazine0.1–0.3 mg/d	cariprazine1 - 2 mg/d
ADT	1	2.428 (1.651, 3.571)	1.702 (1.277, 2.269)	1.568 (0.832, 2.992)	1.482 (1.143, 1.923)	1.779 (1.197, 2.654)	1.281 (0.72, 2.28)	1.694 (1.192, 2.43)
aripiprazole3 - 12 mg/d	0.412 (0.28, 0.606)	1	0.7 (0.416, 1.181)	0.646 (0.31, 1.368)	0.61 (0.37, 1.007)	0.733 (0.416, 1.292)	0.527 (0.24, 1.149)	0.697 (0.373, 1.309)
brexpiprazole1 mg/d	0.588 (0.441, 0.783)	1.428 (0.847, 2.405)	1	0.92 (0.455, 1.881)	0.87 (0.636, 1.191)	1.045 (0.706, 1.548)	0.751 (0.407, 1.39)	0.994 (0.659, 1.507)
brexpiprazole2 - 3 mg/d	0.638 (0.334, 1.201)	1.549 (0.731, 3.229)	1.087 (0.532, 2.195)	1	0.944 (0.469, 1.882)	1.131 (0.528, 2.416)	0.816 (0.344, 1.937)	1.077 (0.517, 2.262)
brexpiprazole2 mg/d	0.675 (0.52, 0.875)	1.638 (0.993, 2.703)	1.15 (0.84, 1.573)	1.06 (0.531, 2.13)	1	1.199 (0.767, 1.881)	0.865 (0.471, 1.594)	1.141 (0.765, 1.723)
brexpiprazole3 mg/d	0.562 (0.377, 0.836)	1.364 (0.774, 2.403)	0.957 (0.646, 1.415)	0.885 (0.414, 1.893)	0.834 (0.532, 1.305)	1	0.719 (0.36, 1.446)	0.952 (0.566, 1.608)
Cariprazine0.1–0.3 mg/d	0.781 (0.439, 1.388)	1.899 (0.87, 4.16)	1.331 (0.719, 2.46)	1.225 (0.516, 2.911)	1.157 (0.627, 2.125)	1.391 (0.692, 2.775)	1	1.323 (0.779, 2.228)
Cariprazine1 - 2 mg/d	0.59 (0.412, 0.839)	1.434 (0.764, 2.685)	1.006 (0.664, 1.518)	0.929 (0.442, 1.936)	0.876 (0.58, 1.307)	1.05 (0.622, 1.768)	0.756 (0.449, 1.284)	1
Cariprazine1.5–4.5 mg/d	0.581 (0.42, 0.805)	1.411 (0.767, 2.615)	0.991 (0.672, 1.46)	0.913 (0.443, 1.887)	0.863 (0.589, 1.261)	1.036 (0.625, 1.71)	0.744 (0.429, 1.297)	0.985 (0.744, 1.309)
Cariprazine1.5 mg/d	0.814 (0.583, 1.133)	1.977 (1.204, 3.235)	1.385 (0.887, 2.167)	1.278 (0.626, 2.622)	1.206 (0.785, 1.853)	1.444 (0.865, 2.44)	1.042 (0.531, 2.051)	1.378 (0.836, 2.288)
Cariprazine3 mg/d	0.746 (0.536, 1.039)	1.811 (1.106, 2.975)	1.27 (0.815, 1.978)	1.171 (0.573, 2.43)	1.106 (0.722, 1.696)	1.325 (0.795, 2.23)	0.957 (0.486, 1.87)	1.264 (0.764, 2.074)
quetiapineXR150 - 300 mg/d	0.846 (0.413, 1.723)	2.062 (0.921, 4.576)	1.439 (0.663, 3.138)	1.328 (0.662, 2.69)	1.253 (0.583, 2.705)	1.502 (0.664, 3.435)	1.086 (0.431, 2.763)	1.435 (0.642, 3.249)
rispridone0.5 - 3 mg/d	0.413 (0.156, 1.099)	1.003 (0.383, 2.644)	0.701 (0.249, 2.01)	0.645 (0.207, 2.122)	0.611 (0.219, 1.719)	0.733 (0.253, 2.141)	0.527 (0.162, 1.743)	0.697 (0.232, 2.119)
rispridone1 - 2 mg/d	0.487 (0.308, 0.772)	1.184 (0.697, 2.002)	0.83 (0.471, 1.463)	0.764 (0.35, 1.687)	0.722 (0.418, 1.255)	0.866 (0.469, 1.606)	0.624 (0.285, 1.374)	0.824 (0.437, 1.579)
Ziprasidon160 mg/d	0.18 (0.025, 1.265)	0.435 (0.057, 3.311)	0.307 (0.042, 2.184)	0.283 (0.036, 2.223)	0.266 (0.037, 1.907)	0.319 (0.044, 2.322)	0.23 (0.031, 1.73)	0.306 (0.042, 2.131)
Ziprasidon80 mg/d	0.959 (0.117, 8.044)	2.333 (0.268, 20.871)	1.633 (0.195, 13.848)	1.515 (0.169, 13.956)	1.42 (0.173, 12.086)	1.712 (0.199, 14.779)	1.226 (0.141, 10.963)	1.629 (0.195, 13.728)

	cariprazine1.5–4.5 mg/d	cariprazine1.5 mg/d	cariprazine3 mg/d	quetiapineXR150 - 300 mg/d	rispridone0.5 - 3 mg/d	rispridone1 - 2 mg/d	ziprasidon160 mg/d	ziprasidon80 mg/d
ADT	1.72 (1.243, 2.379)	1.229 (0.883, 1.714)	1.341 (0.962, 1.866)	1.182 (0.581, 2.42)	2.422 (0.91, 6.402)	2.052 (1.295, 3.248)	5.568 (0.79, 39.639)	1.043 (0.124, 8.524)
aripiprazole3 - 12 mg/d	0.709 (0.382, 1.304)	0.506 (0.309, 0.831)	0.552 (0.336, 0.904)	0.485 (0.219, 1.086)	0.997 (0.378, 2.61)	0.844 (0.5, 1.434)	2.297 (0.302, 17.471)	0.429 (0.048, 3.73)

Table 4 (continued)

	cariprazine1.5–4.5 mg/d	cariprazine1.5 mg/d	cariprazine3 mg/d	quetiapineXR150 - 300 mg/d	rispridone0.5 - 3 mg/d	rispridone1 - 2 mg/d	ziprasidon160 mg/d	ziprasidon80 mg/d
brexpiprazole1 mg/d	1.009 (0.685, 1.489)	0.722 (0.462, 1.127)	0.787 (0.506, 1.228)	0.695 (0.319, 1.509)	1.426 (0.498, 4.018)	1.204 (0.684, 2.125)	3.262 (0.458, 23.56)	0.612 (0.072, 5.118)
brexpiprazole2 - 3 mg/d	1.095 (0.53, 2.258)	0.782 (0.381, 1.598)	0.854 (0.412, 1.744)	0.753 (0.372, 1.51)	1.55 (0.471, 4.834)	1.31 (0.593, 2.857)	3.532 (0.45, 27.625)	0.66 (0.072, 5.904)
brexpiprazole2 mg/d	1.159 (0.793, 1.697)	0.829 (0.54, 1.274)	0.904 (0.59, 1.385)	0.798 (0.37, 1.716)	1.636 (0.582, 4.563)	1.385 (0.797, 2.394)	3.759 (0.524, 26.991)	0.704 (0.083, 5.794)
brexpiprazole3 mg/d	0.966 (0.585, 1.6)	0.692 (0.41, 1.157)	0.755 (0.448, 1.258)	0.666 (0.291, 1.506)	1.364 (0.467, 3.951)	1.155 (0.623, 2.13)	3.131 (0.431, 22.891)	0.584 (0.068, 5.013)
Cariprazine0.1–0.3 mg/d	1.344 (0.771, 2.332)	0.96 (0.488, 1.884)	1.045 (0.535, 2.058)	0.921 (0.362, 2.322)	1.897 (0.574, 6.16)	1.602 (0.728, 3.507)	4.351 (0.578, 32.416)	0.816 (0.091, 7.103)
Cariprazine1 - 2 mg/d	1.015 (0.764, 1.343)	0.726 (0.437, 1.196)	0.791 (0.482, 1.308)	0.697 (0.308, 1.558)	1.434 (0.472, 4.309)	1.214 (0.633, 2.29)	3.266 (0.469, 23.792)	0.614 (0.073, 5.135)
Cariprazine1.5–4.5 mg/d	1	0.716 (0.441, 1.154)	0.78 (0.484, 1.257)	0.688 (0.309, 1.523)	1.412 (0.472, 4.233)	1.195 (0.638, 2.224)	3.241 (0.464, 23.035)	0.606 (0.071, 5.004)
Cariprazine1.5 mg/d	1.397 (0.867, 2.267)	1	1.091 (0.786, 1.519)	0.963 (0.44, 2.102)	1.967 (0.705, 5.393)	1.673 (0.953, 2.911)	4.51 (0.614, 33.427)	0.85 (0.099, 7.215)
Cariprazine3 mg/d	1.282 (0.796, 2.066)	0.917 (0.658, 1.272)	1	0.881 (0.404, 1.938)	1.808 (0.647, 4.954)	1.533 (0.868, 2.687)	4.151 (0.57, 30.121)	0.778 (0.09, 6.617)
quetiapineXR150 - 300 mg/d	1.452 (0.657, 3.241)	1.039 (0.476, 2.275)	1.135 (0.516, 2.477)	1	2.062 (0.606, 6.825)	1.736 (0.741, 4.044)	4.71 (0.576, 38.159)	0.875 (0.092, 8.022)
rispridone0.5 - 3 mg/d	0.708 (0.236, 2.121)	0.509 (0.185, 1.419)	0.553 (0.202, 1.545)	0.485 (0.147, 1.65)	1	0.849 (0.302, 2.365)	2.292 (0.251, 21.563)	0.428 (0.04, 4.604)
rispridone1 - 2 mg/d	0.837 (0.45, 1.568)	0.598 (0.344, 1.049)	0.652 (0.372, 1.152)	0.576 (0.247, 1.349)	1.178 (0.423, 3.308)	1	2.699 (0.359, 20.46)	0.506 (0.057, 4.463)
Ziprasidon160 mg/d	0.309 (0.043, 2.154)	0.222 (0.03, 1.627)	0.241 (0.033, 1.755)	0.212 (0.026, 1.736)	0.436 (0.046, 3.99)	0.371 (0.049, 2.784)	1	0.184 (0.027, 1.286)
Ziprasidon80 mg/d	1.651 (0.2, 14.039)	1.176 (0.139, 10.113)	1.286 (0.151, 11.157)	1.143 (0.125, 10.872)	2.334 (0.217, 25.171)	1.976 (0.224, 17.696)	5.433 (0.777, 37.584)	1

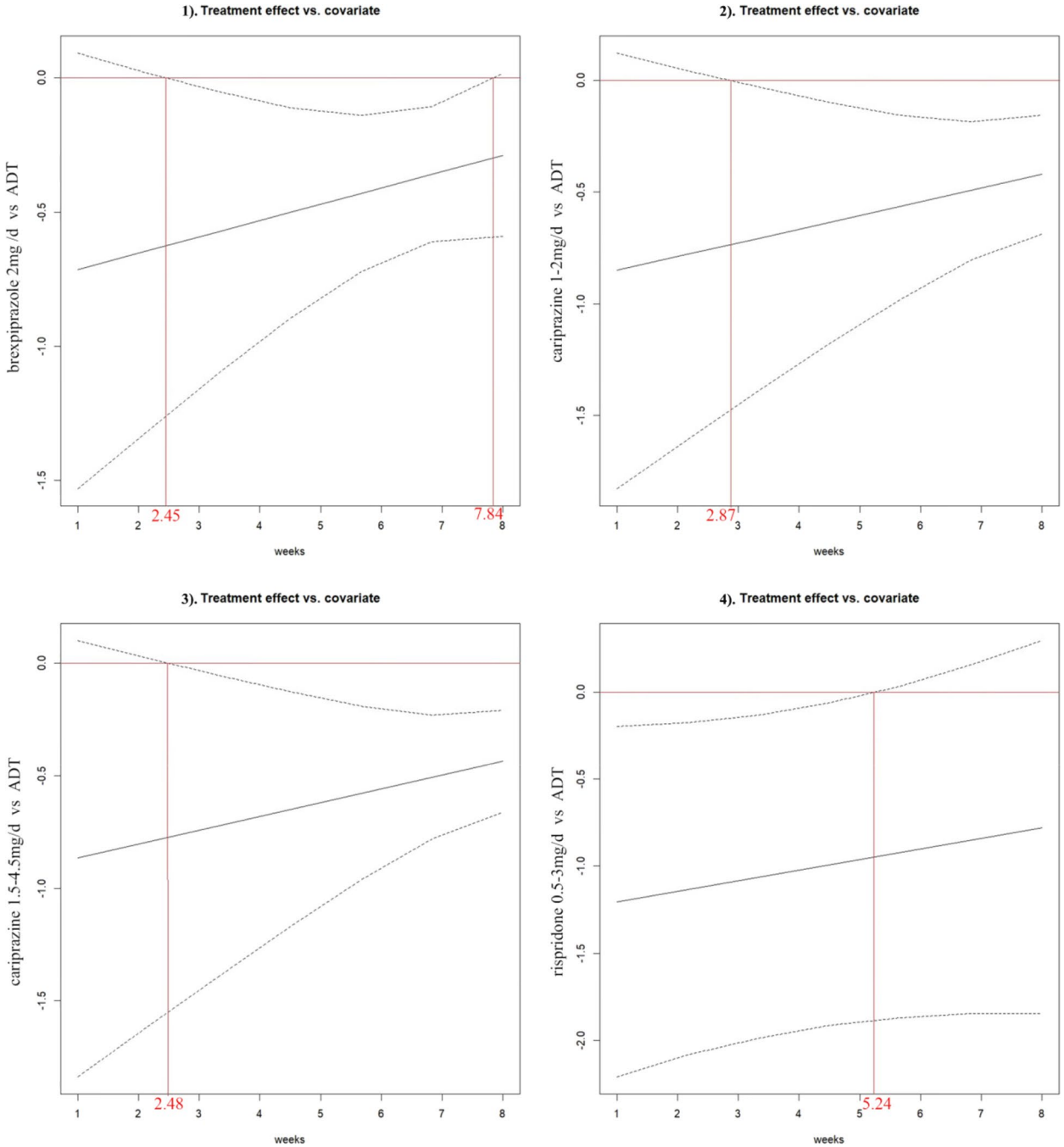

Fig. 5 Time-effect size curves of MADRS response rate

It is widely acknowledged that the combination of fluoxetine and olanzapine resulted in a greater improvement in MDD [46, 47]. However, our results showed that the efficacy of olanzapine diminished after 4.11 weeks. The possible reasons may be as follows: olanzapine has a synergistic effect with fluoxetine, while olanzapine has a weaker synergistic effect with other anti-depressants, leading to the differential outcome [48]. In addition, the main side effects of olanzapine are weight gain and hyperlipidemia, which may compromise the compliance of patients and increase the withdrawal rate, leading to unsatisfying efficacy [49]. Therefore, since the specification of combination of olanzapine and fluoxetine is different from olanzapine (the dosage of olanzapine is less

in the former), this may account for the issue raised in this beginning of this paragraph.

Clinical feasibility analysis

As scrupulously analyzed above, aripiprazole is regarded to be ideal in small doses without"time window". However, in clinical settings, more concern should be addressed. For instance, a percentage patients may undergo extrapyramidal side effects including cathisophobia administrating aripiprazole, a meta-analysis from sages revealed amelioration by using benzhexol [50]. As for the affordability, since aripiprazole has been enrolled in the China National Drug List of Basic Medical Insurance, Work Injury Insurance and Maternity Insurance (2023), therefore it can be reimbursed, paving the way for accessibility [51].

Limitation

Firstly, the sample sizes of certain studies were small, which may result in larger random error, numerically wider 95% confidence intervals, potentially compromising our results.

Secondly, the follow-up periods across enrolled studies were not broad and disperse, hence the underlying"time window"of certain regimens may not emerge in our study and the"time window"calculated may not be quite precise.

Thirdly, we did not include non-pharmacological treatments owing to the limitation of text, which may overestimate the effect of singular SGA use.

Finally, at statistical level, there were several confounders at baseline could have been adjusted, but based on the existing methodology, we could only adjust one confounder in each network meta-regression analysis.

Conclusion

Based on comprehensive consideration, aripiprazole may be the best recommendation among second-generation antipsychotics for augmentation therapy with anti-depressants in treatment-resistant depression, which could be considered in the formulation of clinical guidelines. More head-to-head and long-term studies were necessitated.

Abbreviations

MDD	Major Depressive Disorder
TRD	Treatment-resistant Depression
SGA	Second Generation Antipsychotics
ADT	Anti-depression Therapy
CANMAT	Canadian Network for Mood and Anxiety Treatments
NMR	Network Meta-regression
PRISMA	Preferred Reporting Items for Systematic Review and Meta-analysis
DSM- 5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ICD- 10	The International Statistical Classification of Diseases and Related Health Problems
MADRS	Montgomery Asberg Depression rating scale
CGI-S	Clinical Global Impression-severity
SMD	Standard Mean Difference
HR	Hazard Ratio
SUCRA	Surface Under the Cumulative Ranking Curve
MCMC	Markov Chain Monte Carlo
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
CINeMA	Confidence-In-Network-Meta-Analysis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06783-7.

Supplementary Material 1

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Human and animal rights

Not applicable.

Clinical trial number

Not applicable.

Authors' contributions

B.B. and X.C. designed the study and developed the retrieve strategy. B.B. and Y.L. executed the systematic evaluation as the first and second reviewers, searching and screening the summaries and titles, assessing the inclusion and exclusion criteria, generating data collection forms and extracting data, and evaluating the quality of the study. X.D., C.H. and Y.Y. performed Bayesian network meta-analysis and network meta-regression. B.B. drafted the article, which was reviewed and revised by J.H. and Q.C..

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Data availability

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

NA.

Competing interests

The authors declare no competing interests.

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