Review
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Augmentation Strategies for Partial or Non-responders to Clozapine in Patients with Schizophrenia: A Bayesian Network Meta-analysis of Randomized Controlled Trials

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Clozapine is the only approved drug for treatment-resistant schizophrenia, but the response to the drug is often inadequate. Augmentation with other antipsychotics, anticonvulsants, and antidepressants is recommended for such patients, but there is a lack of evidence regarding the most effective therapy. This network meta-analysis was conducted to evaluate the efficacy of pharmacological agents used in the augmentation strategies in patients who were partial/non-responders to clozapine. Relevant data were extracted from 30 randomized controlled trials through searches of electronic databases (MEDLINE/PubMed, Embase, Cochrane, clinical trial registries). PRISMA guidelines were followed for the extraction, management, analysis, and reporting of the data. The outcome measure in this study was a reduction in symptom severity according to total PANSS/BPRS and was reported as the standardized mean difference with a 95% credible interval. Bayesian network meta-analysis with random effects model and uninformative priors was conducted, and the ranking probability of each intervention was done. Meta-regression was done to assess the effect of duration on the reduction in symptom severity scores. Mirtazapine (−5.2 [95%CrI: −7.7, −2.7]) and memantine (−2.1 [95%CrI: −4.0, −0.19]) were more efficacious than placebo for augmentation of clozapine in partial/non-responders and were the most effective adjunctive agents as per SUCRA scores. Both drugs did not cause a significant increase in frequency of adverse events compared to placebo. There was a significant effect of duration on the reduction in symptom severity. There was no evident publication bias. Mirtazapine and memantine may prove beneficial for augmentation of clozapine in non/partial responders to monotherapy.

KEY WORDS: Clozapine; Schizophrenia; Clozapine-resistant; Augmentation therapy.

INTRODUCTION

Treatment of resistant schizophrenia remains an underachieved goal despite the availability of a number of typical and atypical antipsychotics [1,2]. Clozapine is the only antipsychotic which has been formally approved for the treatment of refractory cases, but an adequate response is evidenced in only 30−60% of patients, thus affecting the quality of life of the patients and caregivers [3,4]. Clozapine has a lower affinity for striatal D2 receptors when compared to most other antipsychotics and, even at maximally tolerated doses, occupies < 65% of these receptors; thus, it is hypothesized to lead to residual symptoms [5].

Patients who are resistant to clozapine therapy despite achieving desired plasma concentrations are termed patients with ultra-resistant schizophrenia. There are several hypotheses defining the pathophysiological pathway of non-responders or partial responders. Dysfunction of glutamatergic transmission, redox disequilibrium, and dopamine receptor supersensitivity are a few of them [6]. Thus, it is postulated that refractory patients may benefit from the modulation of complementary receptor binding pathways.

Augmentation of clozapine with other drugs has been proposed with the objective of broadening the pharmaco-

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dynamic profile of clozapine. Moreover, the drug for augmentation should be chosen so as not to compound the adverse effects such as agranulocytosis, seizures, cardiomyopathy, and adverse metabolic effects. Prescription of two or more antipsychotics seems to be the most sought-after strategy as they enhance the effect by synergistic antipsychotic potency [7]. However, antipsychotic polypharmacy may enhance adverse metabolic effects. There are a few drugs, like anticonvulsants, antidepressants, other antipsychotics, etc., that have been tried as augmentation strategies to treat persistent residual symptoms which compromise the quality of life of patients and caregivers. Most evidence on these drugs comes from case reports, and observational studies with testimony of the effectiveness remaining contradictory or inconclusive. There are a few randomized controlled trials to assess pharmacological augmentation to clozapine, but the order of preference of the drugs could not be ascertained as head-on comparisons are not available. Thus, this network meta-analysis (NMA) was planned to evaluate the efficacy of pharmacological agents used as augmentation strategies in patients who were partial responders or refractory to clozapine.

METHODS

Protocol Development and Registration

A standard network meta-analysis protocol was developed following preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidelines and registered in the international prospective register of ongoing systematic reviews (ROSPERO: CRD42022380302), and was submitted to the institutional ethics committee for a waiver [8]. This network meta-analysis has been conducted and reported in conformance to the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions (PRISMA-NMA) statement [9].

The protocol of the meta-analysis was exempted from the full review and approved by the Institutional Ethics Committee, All India Institute of Medical Sciences (AIIMS), Bhubaneswar, as per ICMR National ethical guidelines (2017) for biomedical and health research (IEC Approval No. T/IM-NF/Pharm/22/135).

Search Strategy

MEDLINE/PubMed, Embase, Google Scholar, Cochrane clinical trial registry and the international clinical trials registry platform (ICTRP) were searched for randomized controlled trials (RCTs) on clozapine in patients with treatment-resistant schizophrenia published until December 2022. Search terms for PubMed and Embase were constructed using terms for disease, the drug clozapine and the terms for response or non-response connected with Boolean operators ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia s"[All Fields]) AND "Clozapine"[Title] AND ("response"[All Fields] OR "responses"[All Fields] OR ("non-response"[All Fields] OR "non-responses"[All Fields] OR "nonresponsive"[All Fields] OR "nonresponsiveness"[All Fields]) OR "non-responder"[All Fields]). The list of references for the published studies was searched for possible inclusions, and the ICTRP was checked for unpublished data.

Study Selection Criteria

RCTs on pharmacological augmentation for partial or non-responders to clozapine therapy for schizophrenia were considered for inclusion. Change in symptom severity as determined by positive and negative symptom scale (PANSS) scores or its equivalent was the primary outcome measure. The studies included either PANSS or a brief psychiatric rating scale (BPRS) as an outcome measure. All studies published in peer-reviewed English language journals, irrespective of the date of publication, place of study or the ethnicity of the study population, were included for analysis. Case reports, case series and letters to the editor were excluded. Studies where "non-response", or "partial response", or "persistent symptoms despite clozapine therapy" were not mentioned were excluded.

Types of participants and intervention

We included studies with patients of either sex of age more than 18 years, diagnosed with schizophrenia as per the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III/IV/V, and were partial responders or non-responders to clozapine therapy. Any pharmacological agent given as an add-on to clozapine therapy was considered a test intervention, and a placebo or any other pharmacological agent was taken as control.

Type of outcomes

The efficacy outcome chosen for this network meta-analysis was a change in PANSS or BPRS. The studies which reported a change in schizophrenia symptoms rating scales (PANSS or BPRS) irrespective of the study duration were included for further analysis.

Study Selection and Data Collection

The eligibility criteria for studies to be included in this network meta-analysis were laid down *a priori*. The selection of the studies for data extraction was made in a stepwise manner. First of all, the title and abstracts of the articles found in the database search were screened as per eligibility criteria. Next, the full text of the selected articles was retrieved and read extensively. Finally, we were left with the articles eligible for extraction of relevant data to be used in this network meta-analysis. Three reviewers (AM, RM, BRM) independently searched the databases for the selection of eligible studies, and any disagreement was resolved in consultation with the fourth reviewer (AS).

Data Extraction and Management

A predefined format was used by the reviewers (AM, RM, BRM) to extract all relevant data from all eligible studies. After data independent data extraction, they discussed their findings, and discrepancies were sorted by a discussion with another reviewer (AS). The data included study design, population studied, intervention, comparator, duration of therapy, sample size, risk of bias and effect estimates. Wherever data was available in the form of plots only, a plot digitizer was used [10]. The safety data for the interventions, which were compared to be better than the placebo, was evaluated qualitatively.

Data Analysis

The data for analysis were represented treatment arm-wise (long data) for Bayesian network meta-analysis. The analysis was performed in R studio using gemtc package in R language [11]. A network plot was created, and the geometry of the network was assessed for connections between pharmacotherapy and individual trials. Markov chain Monte Carlo simulations were used to synthesize pooled treatment effects from non-informative priors using random-effects variance consistency models. The convergence of models using various permutation-combination of burn-in and inference iterations was checked by Brooks-Gelman-Rubin diagnostic tool. A potential scale reduction factor of 1.0009 was obtained, depicting optimal convergence for a combination of burn-in iteration of 5,000 and inference iterations of 100,000. Time series and density plots were used to confirm the findings of convergence. Analysis of leverage statistics and residual deviance was done to ascertain the consistency of the model. The best-fit model was evaluated by the lowest values for deviance information criteria for the Markov Chain Monte Carlo simulations. The relative effects of the pharmacological agents in comparison to the placebo were plotted. Relative effects of treatment in comparison to all the other interventions were tabulated in a relative effects table. The probability ranking of each pharmacological agent was plotted. A global test based on random effects design-by-treatment interaction model was also done to assess incoherence. The surface under cumulative ranking (SUCRA) scores were calculated to determine the probability of each treatment being the best for change in the severity scores of patients. Node-splitting analysis was done for closed triangles in the network plot. The validity of the consistency assumption was further tested by comparison between the direct and indirect evidence for the same comparison. Meta-regression was done to evaluate the effect of the duration of treatment on the relative effect estimates.

Risk of Bias Assessment

Risk of bias assessment tool 2 (RoB2) from Cochrane Collaboration was used to assess the bias in five domains (bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result) [12]. The algorithm for each domain points towards a classification of low risk, some concerns and a high risk of bias. A cumulative judgement for the domains within a study leads to an overall risk-of-bias judgment. Judgement for risk of bias was evaluated independently by three reviewers (AM, RM, BRM), and points of dispute were sorted in consultation with a fourth reviewer (AS). Publication bias was assessed by comparison-adjusted funnel plot visually and Egger's regression test statistically.

Quality of Evidence

The certainty of evidence from each comparison was rated for study design, risk of bias, indirectness, inconsistency, imprecision and publication bias for direct and indirect estimates using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach. Higher of the two qualities available was used for the quality rating of the NMA estimate. Wherever only direct or indirect evidence was available, the quality of the NMA estimate was based on that estimate.

RESULTS

Study Results and Study Characteristics

A total of 30 RCTs were included in this network meta-analysis after screening the databases as per predefined eligibility criteria [13-42]. Some of the studies which did not report improvement in total PANSS or BPRS scores were excluded [43-46]. Similarly, the studies where randomization was not performed were also excluded [47,48]. The study selection process has been represented in the PRISMA flow diagram (Fig. 1). The characteristics of individual studies have been mentioned in Table 1. Risk of bias assessment has been done using the RoB2 tool and is represented in Table 2.

Summary of Network

In this network meta-analysis, 30 studies, including 1,335 patients who were non-responders or partial responders to clozapine therapy, were included. A total of

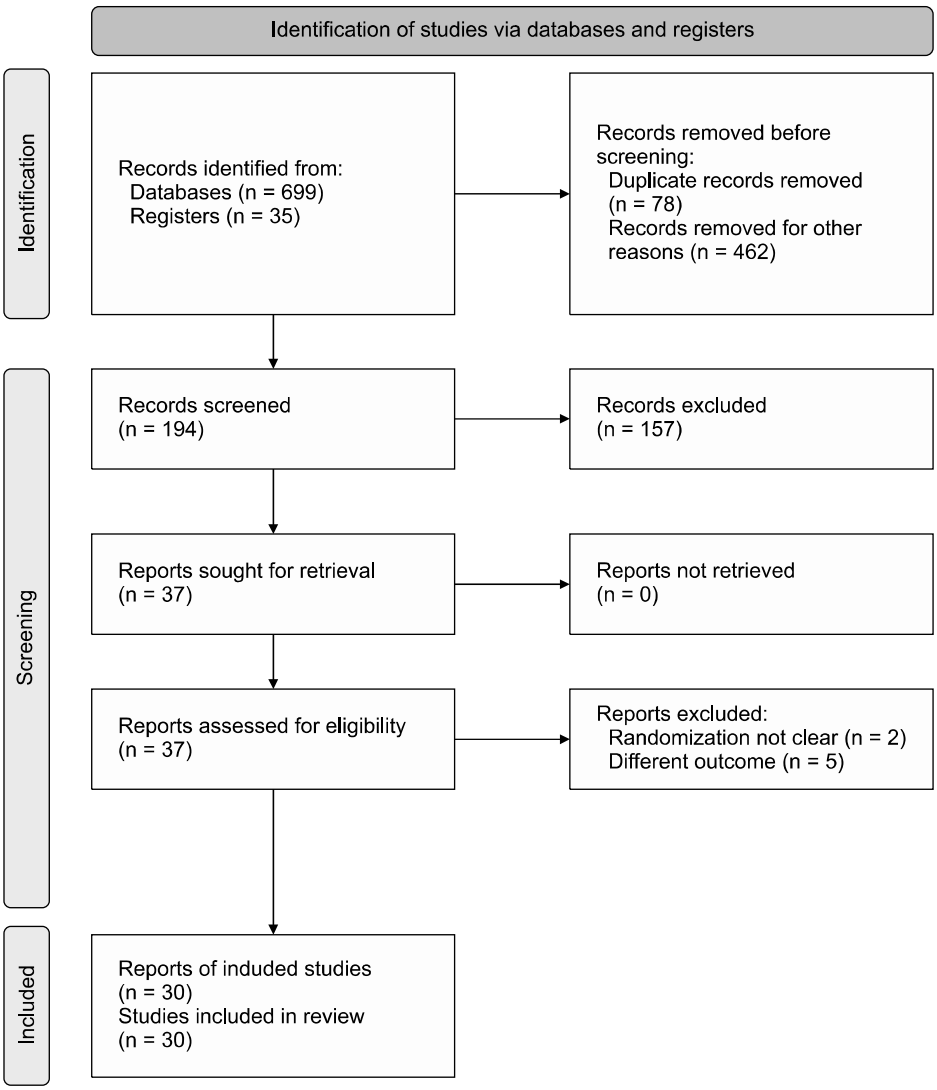

Fig. 1. PRISMA flow diagram for the study selection process.
PRISMA, preferred reporting items for systematic review and meta-analysis protocols.

Table 1. Study characteristics of the included studies

Sl. No	Trial and location	Study design	Participants	Interventions & number of participants	Duration of therapy	Outcomes	Notes/ remarks
1.	Anil Yağcioğlu *et al.* 2005 [13], Turkey	Randomized, double-blind, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Persistent symptoms despite 2 antipsychotic trial prior to clozapine and treated with clozapine monotherapy for at least 6 months and had inadequate response	Clozapine + Risperidone = 16 Clozapine + Placebo = 14	6 weeks	PANSS CGI-S UKU side effect rating scale CDSS GAF	No significant difference found between the groups
2.	Assion *et al.* 2008 [14], Germany	Randomized, double-blind, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Persistent symptoms despite an adequate trial of clozapine for at least 3 months	Clozapine + Amisulpride = 6 Clozapine + Placebo = 3	6 weeks	BPRS GAF MADRS CGI	Improvement in global outcomes with amisulpride
3.	Barbui *et al.* 2011 [15], Italy	Parallel-group, randomized controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Failed at least to 2 antipsychotic trial prior to clozapine and treated with clozapine monotherapy for at least 6 months and unsatisfactory response	Clozapine + Haloperidol = 53 Clozapine + Aripiprazole = 53	3 months	BPRS LUNSERS	Augmentation with haloperidol is not significantly different aripiprazole
4.	Barnes *et al.* 2017 [16], United Kingdom	Randomized double-blind, parallel-group, placebo-controlled trial	Persistent symptoms despite treatment with clozapine for at least 12 weeks	Clozapine + Amisulpride = 35 Clozapine + Placebo = 33	12 weeks	PANSS CDSS SOFAS	There was no significant difference between amisulpride and placebo groups
5.	Chang *et al.* 2008 [17], Republic of Korea	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Failed at least to 2 antipsychotic trial prior to clozapine and treated with clozapine monotherapy for at least 1 year and had shown unsatisfactory response	Clozapine + Aripiprazole = 29 Clozapine + Placebo = 32	8 weeks	BPRS SANS YBOCS MADRS UKU side effect rating scale	A favourable effect in negative symptoms was observed with aripiprazole
6.	de Lucena *et al.* 2009 [18], Brazil	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; On clozapine treatment over last 10 years with partial remission	Clozapine + Memantine = 10 Clozapine + Placebo = 11	12 weeks	BPRS CGI SAS MMSE	Memantine was associated with improvement in refractory schizophrenia
7.	Doruk *et al.* 2008 [19], Turkey	Randomized parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Failed at least to 2 antipsychotic trial prior to clozapine and treated with clozapine monotherapy for at least 6 months and had shown unsatisfactory response	Clozapine + Ginkgo biloba = 20 Clozapine + Placebo = 22	12 weeks	BPRS SAPS SANS	Ginkgo biloba was effective in decreasing negative symptoms but not overall symptoms
8.	Freudenreich *et al.* 2007 [20], USA	Randomized parallel-group, double-blind, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Failed at least to 2 antipsychotic trial prior to clozapine and treated with clozapine monotherapy for at least 6 months with unsatisfactory response	Clozapine + Risperisone = 11 Clozapine + Placebo = 13	8 weeks	PANSS SANS AIMS	Risperidone did not show any significant benefit over placebo
9.	Friedman *et al.* 2011 [21], USA	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Treatment unresponsive to an adequate trial of clozapine therapy	Clozapine + Pimozide = 25 Clozapine + Placebo = 28	12 weeks	PANSS CGI Safety evaluation	No evidence of benefit from pimozide augmentation

Table 1. Continued 1

Sl. No	Trial and location	Study design	Participants	Interventions & number of participants	Duration of therapy	Outcomes	Notes/ remarks
10.	Genç *et al.* 2007 [22], Turkey	Single-blind, randomized controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Unsatisfactory response despite adequate trial of clozapine for at least 12 weeks	Clozapine + Amisulpride = 27 Clozapine + Quetiapine = 23	8 weeks	BPRS SAPS SANS CGI UKU side effect rating scale	Amisulpride appears to be effective and well tolerated
11.	Gunduz-Bruce *et al.* 2013 [23], USA	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Partial responders to an adequate trial of clozapine	Clozapine + Pimozide = 14 Clozapine + Placebo = 14	12 weeks	BPRS SANS CGI AIMS	Pimozide augmentation did not prove to be an effective strategy
12.	Honer *et al.* 2006 [24], Canada	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Failed at least to 2 antipsychotic trial prior to clozapine and treated with clozapine monotherapy for at least 12 weeks and did not show satisfactory response	Clozapine + Risperidone = 34 Clozapine + Placebo = 34	8 weeks	PANSS CGI Verbal working memory	Risperidone did not improve symptoms in patients
13.	Josiassen *et al.* 2005 [25], USA	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Failed at least to 2 antipsychotic trial prior to clozapine and treated with clozapine monotherapy for at least 3 months and did not show satisfactory response	Clozapine + Risperidone = 20 Clozapine + Placebo = 20	12 weeks	BPRS CGI SANS SAS	Risperidone improved overall symptoms
14.	Kelly *et al.* 2015 [26], USA	Randomized, double-blind, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Persistent symptoms despite an adequate trial of clozapine for at least 6 months	Clozapine + Minocycline = 27 Clozapine + Placebo = 23	10 weeks	BPRS CGI	No significant difference between minocycline and placebo groups
15.	Lane *et al.* 2006 [27], Taiwan	Randomized, double-blind, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Failed at least to 2 antipsychotic trial prior to clozapine and treated with clozapine monotherapy for at least 3 months and had shown inadequate response	Clozapine + Sarcosine = 10 Clozapine + Placebo = 10	6 weeks	PANSS	No improvement with the addition of sarcosine in patients with schizophrenia
16.	Lin *et al.* 2018 [28], Taiwan	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Failed at least to 2 antipsychotic trial prior to clozapine and treated with clozapine monotherapy for at least 6 months and had shown no response	Clozapine + Sodium benzoate = 20 Clozapine + Placebo = 20	6 weeks	PANSS SANS QoLS GAF HAMD-17 Cognitive function	Sodium benzoate improves symptomatology in patients with Clozapine resistance
17.	Lu *et al.* 2018 [29], Taiwan	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Failed at least to 2 antipsychotic trial prior to clozapine and treated with clozapine monotherapy	Clozapine + Fluvoxamine = 43 Clozapine + Placebo = 42	12 weeks	PANSS MADRS Pharmaco-kinetics	Significant reduction in PANSS scores
18.	Mico *et al.* 2011 [30], Italy	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Unsatisfactory response despite an adequate trial of clozapine for at least 1 year	Clozapine + Duloxetine = 20 Clozapine + Placebo = 20	16 weeks	PANSS BPRS CDSS Safety evaluation	Duloxetine showed a beneficial effect
19.	Muscatello *et al.* 2011 [31], Italy	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Unsatisfactory response despite adequate trial of clozapine	Clozapine + Topiramate = 19 Clozapine + Placebo = 24	24 weeks	BPRS CDSS SANS SAPS	Topiramate was scarcely beneficial

Table 1. Continued 2

Sl. No	Trial and location	Study design	Participants	Interventions & number of participants	Duration of therapy	Outcomes	Notes/ remarks
20.	Muscatello *et al.* 2011 [32], Italy	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Unsatisfactory response despite adequate trial of clozapine	Clozapine + Aripiprazole = 14 Clozapine + Placebo = 17	24 weeks	BPRS SAPS SANS CDSS Safety evaluation	Aripiprazole may be beneficial to patients partially responsive to clozapine
21.	Muscatello *et al.* 2014 [33], Italy	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Persistent symptoms despite adequate trial of clozapine for at least 1 year	Clozapine + Ziprasidone = 20 Clozapine + Placebo = 20	16 weeks	PANSS BPRS CDSS Safety evaluation	Ziprasidone was effective on negative and cognitive symptoms
22.	Shiloh *et al.* 1997 [34], Israel	Randomized, double-blind, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Persistent symptoms despite 3 antipsychotic trials prior to clozapine and treated with clozapine monotherapy for at least 12 months and had partial response	Clozapine + Sulpiride = 16 Clozapine + Placebo = 12	10 weeks	BPRS SAPS SANS HAM-D	Sulpiride augmentation shows beneficial effect in partial responders
23.	Tiihonen *et al.* 2003 [35], Finland	Randomized double-blind, placebo-controlled crossover trial	Diagnosed with Schizophrenia according to DSM-IV; Unsatisfactory response despite adequate trial of clozapine for at least 6 months	Clozapine + Lamotrigine = 29 Clozapine + Placebo = 30	14 weeks	PANSS UKU side effect rating scale	Beneficial effect on both positive and general psychopathological symptoms
24.	Vayısoğlu *et al.* 2013 [36], Turkey	Randomized, double-blind, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Persistent symptoms despite an adequate trial of clozapine for at least 1 year	Clozapine + Lamotrigine = 17 Clozapine + Placebo = 17	12 weeks	PANSS CDS CGI-S UKU side effect rating scale	No benefit of lamotrigine over placebo
25.	Weiner *et al.* 2010 [37], USA	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Unsatisfactory response despite adequate trial of clozapine for at least 6 months	Clozapine + Risperidone = 30 Clozapine + Placebo = 34	16 weeks	BPRS SANS CGI	Adjunctive risperidone may have modest benefit
26.	Zhu *et al.* 2022 [38], China	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Failed at least to 2 antipsychotic trial prior to clozapine and treated with clozapine monotherapy for at least 3 months and did not show satisfactory response	Clozapine + Amisulpride = 40 Clozapine + Placebo = 40	12 weeks	PANSS SANS CGI-S CGI-I TESS	Amisulpride augmentation improves symptoms
27.	Zink *et al.* 2009 [39], Germany	Parallel-group Randomized controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Failed at least to 2 antipsychotic trial prior to clozapine and treated with clozapine monotherapy for at least 3 months and had inadequate response	Clozapine + Risperidone = 12 Clozapine + Ziprasidone = 12	6 weeks	PANSS HAMD SANS CGI	Significant psychopathological improvements observed in both the groups
28.	Zoccali *et al.* 2004 [40], Italy	Randomized, double-blind, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Persistent symptoms despite an adequate trial of clozapine for at least 1 year	Clozapine + Mirtazapine = 10 Clozapine + Placebo = 10	8 weeks	BPRS SANS SAPS HAM-D	Suggest a potential role for mirtazapine as an augmentation strategy in schizophrenia
29.	Zoccali *et al.* 2007 [41], Italy	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-IV; Persistent symptoms despite adequate trial of clozapine for at least 1 year	Clozapine + Lamotrigine = 26 Clozapine + Placebo = 25	24 weeks	SANS SAPS BPRS CDSS Stroop test	Lamotrigine showed a beneficial effect

Table 1. Continued 3

Sl. No	Trial and location	Study design	Participants	Interventions & number of participants	Duration of therapy	Outcomes	Notes/ remarks
30.	Evins *et al.* 2000 [42], USA	Randomized double-blind, parallel-group, placebo-controlled trial	Diagnosed with Schizophrenia according to DSM-III; Persistent symptoms despite adequate trial of clozapine for at least 4 weeks	Clozapine + Glycine = 14 Clozapine + Placebo = 13	8 weeks	SANS PANSS BPRS	No significant effect of Glycine

PANSS, positive and negative syndrome scale; BPRS, brief psychiatric rating scale; CGI, clinical global impression scale; SAPS, scale for assessment of positive symptoms; SANS, scale for assessment of negative symptoms; MADRS, Montgomery–Åsberg depression rating scale; HAM-D, Hamilton rating scale for depression; GAF, global functioning assessment; AIMS, abnormal involuntary movement scale; QoLS, quality of life scale; SAS, Simpson-Angus scale; CDSS, Calgary depression scale; LUNSERS, Liverpool University neuroleptic side effect rating scale; UKU side effect rating scale, Udvalg for Kliniske Undersøgelser side effect rating scale; TESS, treatment emergent symptom scale; CDS, cognitive difficulties scale; MMSE, mini-mental state examination; YBOCS, Yale–Brown obsessive compulsive scale; SOFAS, social and occupational functioning assessment scale; DSM, diagnostic and statistical manual of mental disorders.

Table 2. Risk of bias table for included studies

Sl. No	Trial	Randomization process	Deviation from intended intervention	Missing outcome data	Measurement of outcome data	Selection of reported result	Overall judgment
1.	Anil Yağcioğlu *et al.* 2005 [13]	Some concerns	Low	High	Low	Low	Some concerns
2.	Assion *et al.* 2008 [14]	Low	Low	Low	Low	Low	Low
3.	Barbui *et al.* 2011 [15]	Low	Low	Low	Low	Low	Low
4.	Barnes *et al.* 2017 [16]	Low	Low	Low	Low	Some concerns	Some concerns
5.	Chang *et al.* 2008 [17]	Low	Low	Low	Low	Low	Low
6.	de Lucena *et al.* 2009 [18]	Some concerns	Low	Low	Low	Low	Some concerns
7.	Doruk *et al.* 2008 [19]	Some concerns	Low	Low	Low	Low	Some concerns
8.	Freudenreich *et al.* 2007 [20]	Low	Low	Low	Low	Low	Low
9.	Friedman *et al.* 2011 [21]	Some concerns	Low	Low	Low	Low	Some concerns
10.	Genç *et al.* 2007 [22]	Some concerns	High	Low	Low	Low	High
11.	Gunduz-Bruce *et al.* 2013 [23]	Some concerns	Low	Low	Low	Low	Some concerns
12.	Honer *et al.* 2006 [24]	Low	Low	Low	Low	Low	Low
13.	Josiassen *et al.* 2005 [25]	Some concerns	Low	Low	Low	Low	Some concerns
14.	Kelly *et al.* 2015 [26]	Low	Low	Low	Low	Low	Low
15.	Lane *et al.* 2006 [27]	Low	Low	Low	Low	Low	Low
16.	Lin *et al.* 2018 [28]	Low	Low	Low	Low	Low	Low
17.	Lu *et al.* 2018 [29]	Low	Low	Low	Low	Low	Low
18.	Mico *et al.* 2011 [30]	Low	Low	Low	Low	Low	Low
19.	Muscatello *et al.* 2011 [31]	Low	Low	Some concerns	Low	Low	Some concerns
20.	Muscatello *et al.* 2011 [32]	Low	Some concerns	Low	Low	Low	Some concerns
21.	Muscatello *et al.* 2014 [33]	Low	Low	Low	Low	Low	Low
22.	Shiloh *et al.* 1997 [34]	High	Low	Low	Low	Low	High
23.	Tiihonen *et al.* 2003 [35]	Low	Low	Low	Low	Low	Low
24.	Vayısoğlu *et al.* 2013 [36]	Low	Low	Low	Low	Low	Low
25.	Weiner *et al.* 2010 [37]	Some concerns	Low	Low	Low	Low	Some concerns
26.	Zhu *et al.* 2022 [38]	Low	Low	Low	Low	Low	Low
27.	Zink *et al.* 2009 [39]	Some concerns	Low	Low	High	Low	High
28.	Zoccali *et al.* 2004 [40]	Some concerns	Some concerns	Low	Low	Low	Some concerns
29.	Zoccali *et al.* 2007 [41]	Low	Low	Low	Low	Low	Low
30.	Evins *et al.* 2000 [42]	Low	Low	Low	Low	Low	Low

19 interventions have been analyzed cumulatively in the above-mentioned studies. All the studies were two-arm studies except Assion 2008, where two doses of amisulpride were compared against a placebo. However, we have used the higher dose (600 mg/day) for the purpose of this analysis. Network geometry has been plotted and rep-

resented in Figure 2.

Analysis of comparison of all possible interventions

The consistency model was built, which compared all possible pharmacological agents used in the augmentation of clozapine therapy in patients with schizophrenia. Global test based on a random-effects design-by-treatment interaction model yielded a $\chi^2 = 1.297$ ($p = 0.255$), meaning no concerns for incoherence in the NMA. The standardized mean difference and 95% credible interval (95%CrI) of augmentation agent(s) have been determined with respect to all the other agents and have been represented in the relative effects table (Table 3). A relative effect plot was constructed for the effect estimate of all interventions with respect to the placebo (Fig. 3). Mirtazapine (−5.2 [95%CrI: −7.7, −2.7]) and memantine (−2.1 [95%CrI: −4.0, −0.19]) were observed to be more efficacious in the reduction of symptom severity scores when combined with clozapine in non/partial responders to clozapine when compared with placebo. None of the other interventions showed any significant difference in the improvement of the severity of symptoms in comparison to the placebo.

Node-splitting analysis was done for closed triangles in the network plot. The p value for inconsistency in the networks was > 0.05, and thus the direct evidence seems to be consistent with the indirect evidence. The summary plot for node-split analysis is represented in Figure 4. A matrix for the probability of each intervention for every rank was created and plotted; the rank probability matrix has been plotted in Figure 5.

According to the rank probability matrix, the highest probability for the first rank was for mirtazapine, followed by memantine and duloxetine, and for the second rank, the probability was highest for memantine, and duloxetine had the highest probability for third rank. Mirtazapine was observed to have the highest SUCRA score (0.99), followed by memantine (0.86) and duloxetine (0.77). SUCRA score has been represented in a bar plot in Figure 6.

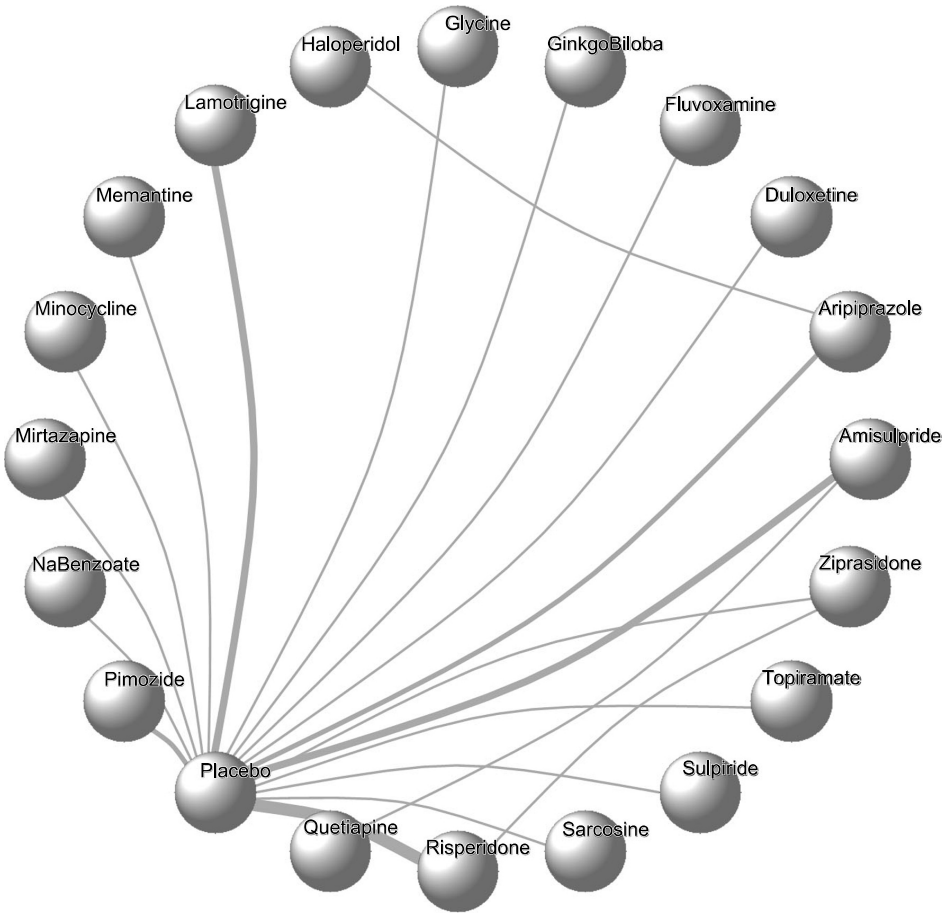

Fig. 2. Network plot of all possible augmentation agents to clozapine.

Table 3. Relative effects table

Amisulpride	0.01 (−1.68, 1.73)	−1.13 (−3.27, 1.02)	0.14 (−1.99, 2.31)	0.15 (−1.97, 2.30)	0.43 (−1.70, 2.61)	0.13 (−2.34, 2.67)	0.02 (−1.49, 1.58)	−1.74 (−3.95, 0.46)	−0.19 (−2.32, 2.00)	−4.83 (−7.53, −2.08)	−0.42 (−2.55, 1.77)	1.06 (−0.65, 2.82)	0.36 (−0.73, 1.48)	0.45 (−1.40, 2.30)	−0.06 (−1.41, 1.29)	0.13 (−2.05, 2.29)	−0.46 (−2.62, 1.70)	−0.06 (−2.20, 2.11)	−0.38 (−2.14, 1.38)
	Aripiprazole	−1.14 (−3.43, 1.10)	0.13 (−2.15, 2.40)	0.14 (−2.12, 2.43)	0.42 (−1.86, 2.68)	0.12 (−1.71, 1.99)	0.01 (−1.67, 1.71)	−1.75 (−4.10, 0.55)	−0.20 (−2.46, 2.06)	−4.84 (−7.66, −2.04)	−0.42 (−2.71, 1.85)	1.05 (−0.79, 2.93)	0.35 (−0.97, 1.65)	0.44 (−2.08, 2.97)	−0.06 (−1.60, 1.43)	0.11 (−2.17, 2.41)	−0.48 (−2.77, 1.81)	−0.06 (−2.33, 2.18)	−0.40 (−2.31, 1.50)
		Duloxetine	1.28 (−1.31, 3.86)	1.30 (−1.31, 3.91)	1.58 (−1.05, 4.18)	1.27 (−1.59, 4.19)	1.16 (−0.95, 3.27)	−0.61 (−3.25, 2.05)	0.95 (−1.66, 3.56)	−3.69 (−6.80, −0.61)	0.72 (−1.90, 3.33)	2.19 (−0.04, 4.50)	1.49 (−0.33, 3.34)	1.59 (−1.24, 4.40)	1.07 (−0.90, 3.06)	1.26 (−1.36, 3.94)	0.67 (−1.94, 3.29)	1.07 (−1.52, 3.68)	0.74 (−1.55, 3.08)
			Fluvoxamine	0.01 (−2.56, 2.61)	0.29 (−2.31, 2.90)	0.00 (−2.90, 2.89)	−0.12 (−2.23, 2.02)	−1.90 (−4.54, 0.76)	−0.34 (−2.92, 2.27)	−4.97 (−8.05, −1.86)	−0.56 (−3.17, 2.07)	0.92 (−1.32, 3.19)	0.21 (−1.63, 2.06)	0.31 (−2.51, 3.12)	−0.20 (−2.18, 1.78)	−0.01 (−2.64, 2.59)	−0.61 (−3.21, 2.01)	−0.20 (−2.83, 2.41)	−0.52 (−2.85, 1.78)
				Ginkgo Biloba	0.27 (−2.31, 2.89)	−0.02 (−2.93, 2.91)	−0.13 (−2.25, 1.98)	−1.90 (−4.56, 0.76)	−0.35 (−2.94, 2.24)	−4.99 (−8.10, −1.87)	−0.57 (−3.18, 2.05)	0.91 (−1.35, 3.16)	0.20 (−1.63, 2.04)	0.29 (−2.53, 3.11)	−0.22 (−2.23, 1.78)	−0.03 (−2.68, 2.59)	−0.62 (−3.24, 1.97)	−0.22 (−2.81, 2.36)	−0.53 (−2.83, 1.75)
					Glycine	−0.29 (−3.21, 2.62)	−0.41 (−2.52, 1.73)	−2.18 (−4.85, 0.48)	−0.63 (−3.21, 1.98)	−5.27 (−8.31, −2.15)	−0.85 (−3.48, 1.75)	0.62 (−1.62, 2.92)	−0.07 (−1.89, 1.78)	0.02 (−2.85, 2.82)	−0.49 (−2.49, 1.52)	−0.30 (−2.95, 2.32)	−0.90 (−3.49, 1.73)	−0.49 (−3.10, 2.12)	−0.82 (−3.14, 1.49)
						Haloperidol	−0.11 (−2.60, 2.37)	−1.88 (−4.86, 1.10)	−0.33 (−3.23, 2.60)	−4.96 (−8.33, −1.59)	−0.56 (−3.50, 2.36)	0.92 (−1.67, 3.54)	0.22 (−2.04, 2.46)	0.31 (−2.83, 3.41)	−0.19 (−2.60, 2.16)	−0.01 (−2.93, 2.89)	−0.60 (−3.54, 2.33)	−0.19 (−3.15, 2.69)	−0.52 (−3.19, 2.11)
							Lamotrigine	−1.77 (−3.96, 0.43)	−0.21 (−2.34, 1.90)	−4.85 (−7.52, −2.13)	−0.44 (−2.58, 1.71)	1.03 (−0.63, 2.75)	0.33 (−0.73, 1.39)	0.43 (−2.01, 2.82)	−0.08 (−1.40, 1.22)	0.10 (−2.05, 2.27)	−0.48 (−2.63, 1.64)	−0.08 (−2.24, 2.03)	−0.41 (−2.17, 1.34)
								Memantine	1.55 (−1.09, 4.21)	−3.08 (−6.24, 0.05)	1.32 (−1.36, 4.01)	2.81 (0.49, 5.16)	2.10 (0.18, 4.03)	2.20 (−0.71, 5.10)	1.68 (−0.39, 3.79)	1.87 (−0.81, 4.51)	1.28 (−1.42, 3.94)	1.68 (−0.98, 4.32)	1.36 (−1.00, 3.73)
									Minocycline	−4.64 (−7.71, −1.52)	−0.23 (−2.82, 2.38)	1.25 (−0.98, 3.51)	0.54 (−1.27, 2.39)	0.64 (−2.20, 3.49)	0.12 (−1.86, 2.13)	0.31 (−2.33, 2.96)	−0.28 (−2.85, 2.32)	0.12 (−2.49, 2.72)	−0.20 (−2.53, 2.12)
										Mirtazapine	4.42 (1.27, 7.47)	5.89 (3.08, 8.72)	5.19 (2.69, 7.66)	5.28 (1.96, 8.57)	4.76 (2.14, 7.35)	4.96 (1.82, 8.08)	4.36 (1.23, 7.42)	4.77 (1.65, 7.82)	4.44 (1.58, 7.26)
											NaBenzoate	1.48 (−0.781, 3.75)	0.78 (−1.07, 2.62)	0.87 (−2.02, 3.71)	0.35 (−1.68, 2.34)	0.54 (−2.10, 3.16)	−0.05 (−2.67, 2.57)	0.36 (−2.27, 2.99)	0.02 (−2.30, 2.346)
												Pimozide	−0.70 (−2.03, 0.60)	−0.60 (−3.20, 1.91)	−1.13 (−2.67, 0.40)	−0.94 (−3.24, 1.35)	−1.53 (−3.81, 0.74)	−1.13 (−3.42, 1.14)	−1.45 (−3.38, 0.44)
													Placebo	0.09 (−2.09, 2.27)	−0.42 (−1.21, 0.35)	−0.23 (−2.11, 1.63)	−0.83 (−2.69, 1.01)	−0.42 (−2.26, 1.41)	−0.74 (−2.13, 0.64)
														Quetiapine	−0.51 (−2.83, 1.78)	−0.32 (−3.16, 2.52)	−0.92 (−3.77, 1.97)	−0.52 (−3.41, 2.36)	−0.84 (−3.41, 1.73)
															Risperidone	0.18 (−1.86, 2.22)	−0.40 (−2.41, 1.60)	0.00 (−2.01, 2.00)	−0.32 (−1.70, 1.07)
																Sarcosine	−0.59 (−3.22, 2.05)	−0.18 (−2.85, 2.46)	−0.51 (−2.87, 1.83)
																	Sulpiride	0.40 (−2.19, 3.05)	0.08 (−2.23, 2.40)
																		Topiramate	−0.32 (−2.62, 2.00)
																			Ziprasidone

Values are presented as standardized mean difference (95% credible interval).
Comparison of column-specific intervention with row-specific interventions.

Meta-regression analysis

Meta-regression was done to assess the effect of duration on the reduction in the severity of symptoms in patients. The analysis showed that there was a significant improvement in the severity of symptoms with increasing duration of therapy (slope: −0.74 [95%CrI: −1.039, −0.438]). The estimates at the centring value of 11.73 weeks for the duration of therapy have been represented in the relative effect plot in Figure 7.

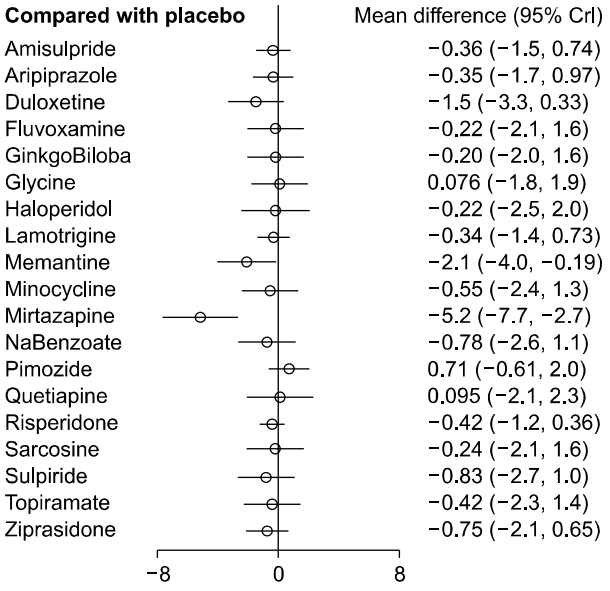

Fig. 3. Relative effects plots. Comparative efficacy of all possible augmentation agents in comparison to placebo in the network meta-analysis.
CrI, credible intervals.

Publication bias

Comparison-adjusted funnel plot was created by plotting standard error against mean difference centred at comparison-specific effect. The plot appeared symmetrical in visual inspection (Fig. 8). This was further corroborated by Egger's test ($p = 0.725$), which was not found to be significant. Thus, we conclude that there was no evident publication bias in this network meta-analysis.

Quality of evidence

Certainty of evidence for all possible comparisons used as augmentation therapy was determined. The evidence was rated as very low to moderate in quality (Table 4). NMA results sorted based on the quality of evidence for a decrease in scores for severity of symptoms for augmentation agents to clozapine when compared with placebo has been tabulated in Table 5.

Safety Evaluation

The safety concerns and safety evaluation parameters were different in each study. There was only one study each per comparison of mirtazapine and memantine to placebo. These studies used different tools to report the adverse event as per the drug-specific safety profile, and thus quantitative analysis was not feasible. A few patients in the mirtazapine group experienced mild drowsiness and weight gain. Three patients receiving a placebo and one receiving memantine complained of dizziness and nausea, while there was no significant difference in extrapyramidal adverse effects and weight gain. All the drugs evaluated in the articles included in this meta-anal-

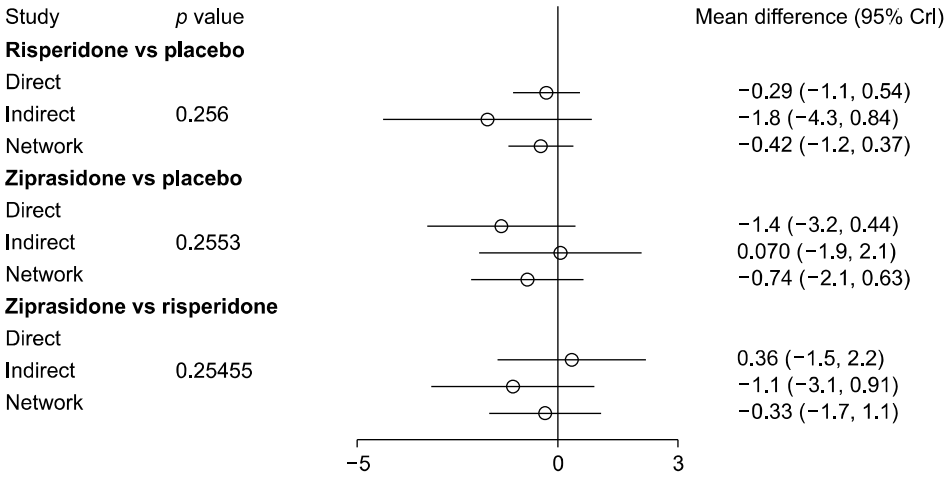

Fig. 4. Node split analysis of all possible interventions forming a closed triangle in the network meta-analysis.
CrI, credible intervals.

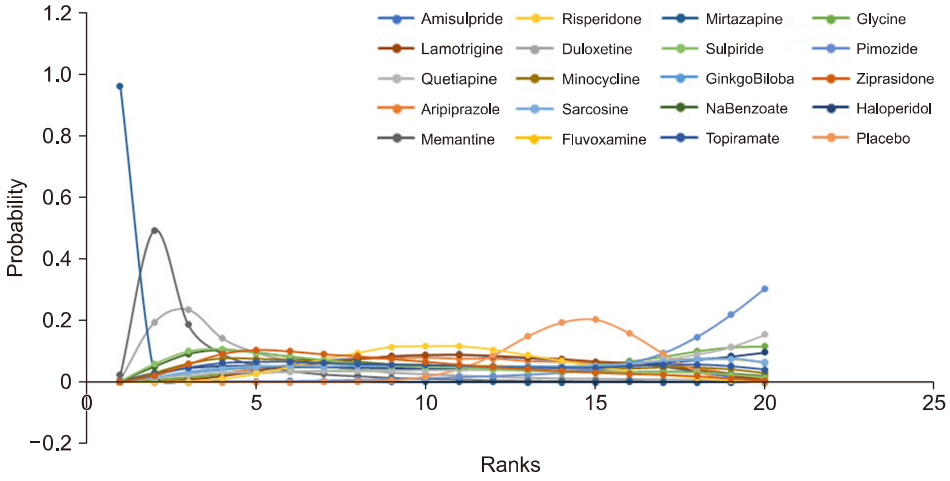

Fig. 5. The rank probability of all augmentation strategies.
SUCRA, surface under cumulative ranking.

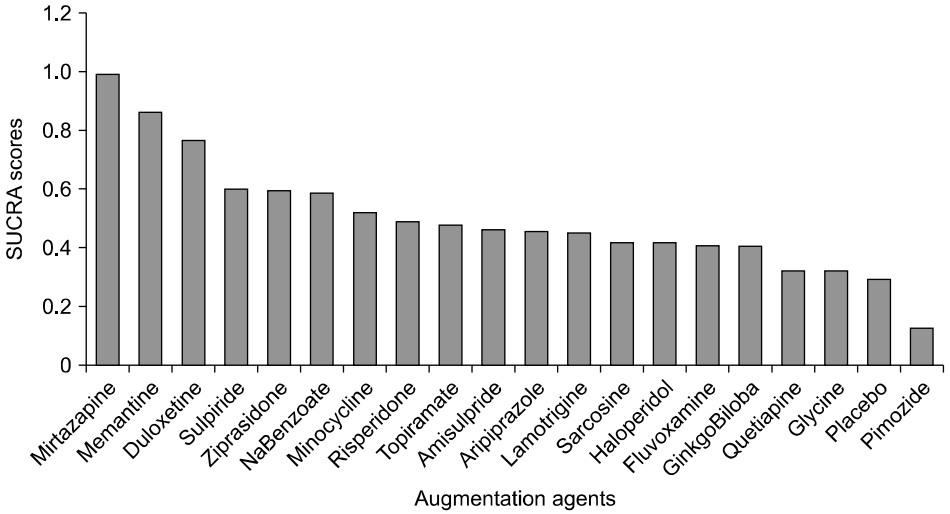

Fig. 6. SUCRA scores of all augmentation strategies.
SUCRA, surface under cumulative ranking.

ysis were well tolerated and did not show any significant increase in adverse events when compared to the placebo. The effect could not be pooled in the absence of a uniform tool across the studies.

DISCUSSION

This network meta-analysis summarizes the effect of interventions employed in 30 RCTs on the reduction in symptom severity scores in patients with schizophrenia who were partial/non-responders to clozapine therapy and were started on pharmacological augmentation. Augmentation of clozapine with mirtazapine and memantine proves to be the most efficacious in patients as per the consistency model of this NMA. It was observed that improvement in symptoms was directly influenced positively by the duration of therapy. The agents were well tolerated with a good safety profile when compared to the placebo.

These agents act through different mechanisms and may provide potential therapeutic options based on the patient's characteristics. It seems possible that a combination of clozapine and mirtazapine exerts a potentiating synergistic action on multiple receptor subtypes and on the neurotransmission system involved in the aetiopathogenesis of resistant symptoms in schizophrenia [40]. Chronic treatment with clozapine has the property of elevating the expression of mGlu5 receptors, which improves glutamatergic transmission by modelling the N-methyl-D-aspartate (NMDA) glutamatergic system [49]. Memantine is a low-affinity uncompetitive NMDA receptor antagonist which blocks activity specifically at

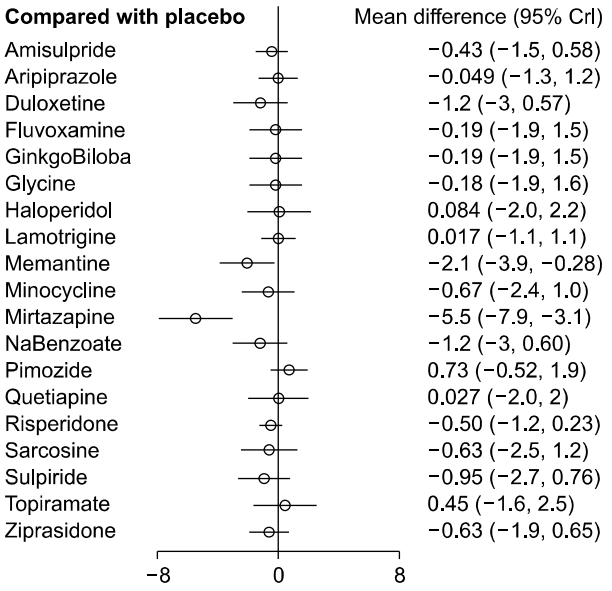

Fig. 7. Relative effects plot for meta-regression. Effect of duration on efficacy outcome in network meta-analysis.
CrI, credible intervals.

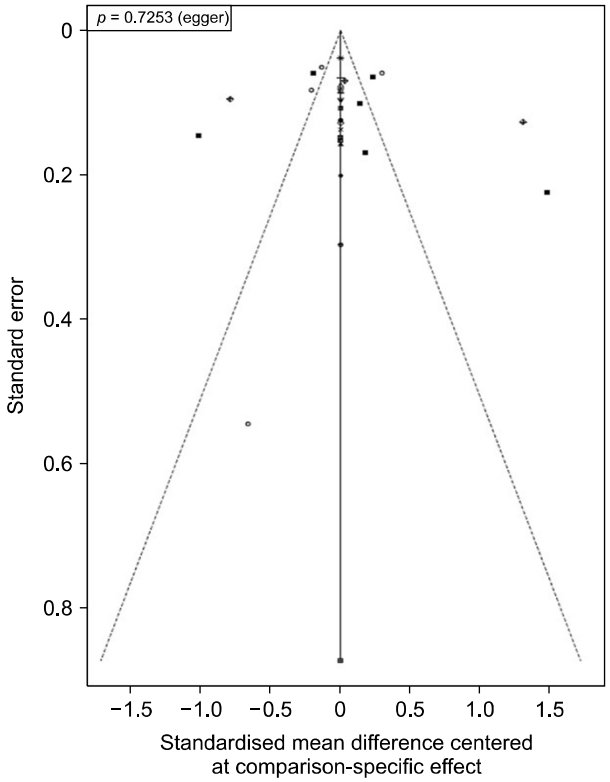

Fig. 8. Comparison adjusted Funnel plot for assessing publication bias.

pathological receptors. The drug may play an important role in the improvement of symptoms in this glutamatergic environment when administered in combination with clozapine [50]. Duloxetine is a potent inhibitor of the reuptake of serotonin and noradrenaline and shows balanced affinity and high selectivity for 5HT transporters [30]. The drug may possess pharmacodynamic synergism with clozapine, and thus a beneficial effect is observed in augmentation therapy. Sulpiride augmentation modulates the interactions between serotonin and dopamine neurotransmitters to achieve a moderate 5HT/D2 ratio, which may be possible for enhanced clinical efficacy when given for adequate duration [34]. Cariprazine, a newer atypical antipsychotic drug, may offer a better tolerated and more acceptable treatment option for partial/non-responders to clozapine, however, presently, no published radomized controlled trial available [51].

This network meta-analysis seemed essential to draw conclusions for therapeutic decisions from all available relevant evidence. As the source of data for result synthesis depends on both direct and indirect evidence, the relative effects obtained for each one of the interventions with respect to the other is interpretable, more robust and reliable. Clozapine is the only approved drug for treatment-resistant schizophrenia, and with only one-third to one-half of the patients responding to the drug, evaluating adjunctive therapy to provide an effective alternative to patients is crucial. None of the antipsychotic augmentation strategies with clozapine outperformed the controls, according to a meta-analysis by Correll *et al.* [52]. In another study by Galling *et al.* [53] it was observed that regardless of whether studies used clozapine or not, there is no proof that antipsychotic augmentation above monotherapy had any further benefits. Thus, augmentation agents involving modulation of another neurotransmission systems like glutamate and serotonin as observed in the results of this meta-analysis would be beneficial. This can be reiterated here that negative and cognitive domains of schizophrenia are the most resistant domains of psychopathology to be addressed with the adjunctive therapies, which could be better managed by targeting serotonin and glutamatergic systems [54].

A network meta-analysis by Yeh *et al.* [55] in patients with clozapine-resistant schizophrenia found that mirtazapine, duloxetine, and memantine were the most efficacious pharmacological augmentation agents, while duloxetine was not found to be more efficacious than placebo. However, the above-cited study was conducted

Table 4. Certainty of evidence for comparisons of all included interventions

Comparison	Direct evidence		Indirect evidence		Network meta-analysis	
	Mean diff (95% CI)	Quality of evidence	Mean diff (95% CrI)	Quality of evidence	Mean diff (95% CrI)	Quality of evidence
Aripiprazole – Amisulpiride	NA	–	0.01 (−1.68, 1.73)	Low	0.01 (−1.68, 1.73)	Low
Duloxetine – Amisulpiride	NA	–	−1.13 (−3.27, 1.02)	Low	−1.13 (−3.27, 1.02)	Low
Fluvoxamine – Amisulpiride	NA	–	0.14 (−1.99, 2.31)	Low	0.14 (−1.99, 2.31)	Low
GinkgoBiloba – Amisulpiride	NA	–	0.15 (−1.97, 2.30)	Low	0.15 (−1.97, 2.30)	Low
Glycine – Amisulpiride	NA	–	0.43 (−1.70, 2.61)	Low	0.43 (−1.70, 2.61)	Low
Haloperidol – Amisulpiride	NA	–	0.13 (−2.34, 2.67)	Low	0.13 (−2.34, 2.67)	Low
Lamotrigine – Amisulpiride	NA	–	0.02 (−1.49, 1.58)	Low	0.02 (−1.49, 1.58)	Low
Memantine – Amisulpiride	NA	–	−1.74 (−3.95, 0.46)	Low	−1.74 (−3.95, 0.46)	Low
Minocycline – Amisulpiride	NA	–	−0.19 (−2.32, 2.00)	Low	−0.19 (−2.32, 2.00)	Low
Mirtazapine – Amisulpiride	NA	–	−4.83 (−7.53, −2.08)	Low	−4.83 (−7.53, −2.08)	Low
NaBenzoate – Amisulpiride	NA	–	−0.42 (−2.55, 1.77)	Low	−0.42 (−2.55, 1.77)	Low
Pimozide – Amisulpiride	NA	–	1.06 (−0.65, 2.82)	Very low	1.06 (−0.65, 2.82)	Very low
Placebo – Amisulpiride	0.36 (−0.73, 1.48)	Low	NE	–	0.36 (−0.73, 1.48)	Low
Quetiapine – Amisulpiride	0.45 (−1.40, 2.30)	Low	NE	–	0.45 (−1.40, 2.30)	Low
Risperidone – Amisulpiride	NA	–	−0.06 (−1.41, 1.29)	Very low	−0.06 (−1.41, 1.29)	Very low
Sarcosine – Amisulpiride	NA	–	0.13 (−2.05, 2.29)	Low	0.13 (−2.05, 2.29)	Low
Sulpiride – Amisulpiride	NA	–	−0.46 (−2.62, 1.70)	Low	−0.46 (−2.62, 1.70)	Low
Topiramate – Amisulpiride	NA	–	−0.06 (−2.20, 2.11)	Low	−0.06 (−2.20, 2.11)	Low
Ziprasidone – Amisulpiride	NA	–	−0.38 (−2.14, 1.38)	Low	−0.38 (−2.14, 1.38)	Low
Duloxetine – Aripiprazole	NA	–	−1.14 (−3.43, 1.10)	Low	−1.14 (−3.43, 1.10)	Low
Fluvoxamine – Aripiprazole	NA	–	0.13 (−2.15, 2.40)	Low	0.13 (−2.15, 2.40)	Low
GinkgoBiloba – Aripiprazole	NA	–	0.14 (−2.12, 2.43)	Low	0.14 (−2.12, 2.43)	Low
Glycine – Aripiprazole	NA	–	0.42 (−1.86, 2.68)	Low	0.42 (−1.86, 2.68)	Low
Haloperidol – Aripiprazole	0.12 (−1.71, 1.99)	Moderate	NE	–	0.12 (−1.71, 1.99)	Moderate
Lamotrigine – Aripiprazole	NA	–	0.01 (−1.67, 1.71)	Low	0.01 (−1.67, 1.71)	Low
Memantine – Aripiprazole	NA	–	−1.75 (−4.10, 0.55)	Low	−1.75 (−4.10, 0.55)	Low
Minocycline – Aripiprazole	NA	–	−0.20 (−2.46, 2.06)	Low	−0.20 (−2.46, 2.06)	Low
Mirtazapine – Aripiprazole	NA	–	−4.84 (−7.66, −2.04)	Low	−4.84 (−7.66, −2.04)	Low
NaBenzoate – Aripiprazole	NA	–	−0.42 (−2.71, 1.85)	Low	−0.42 (−2.71, 1.85)	Low
Pimozide – Aripiprazole	NA	–	1.05 (−0.79, 2.93)	Low	1.05 (−0.79, 2.93)	Low
Placebo – Aripiprazole	0.35 (−0.97, 1.65)	Moderate	NE	–	0.35 (−0.97, 1.65)	Moderate
Quetiapine – Aripiprazole	NA	–	0.44 (−2.08, 2.97)	Low	0.44 (−2.08, 2.97)	Low
Risperidone – Aripiprazole	NA	–	−0.06 (−1.60, 1.43)	Low	−0.06 (−1.60, 1.43)	Low
Sarcosine – Aripiprazole	NA	–	0.11 (−2.17, 2.41)	Low	0.11 (−2.17, 2.41)	Low
Sulpiride – Aripiprazole	NA	–	−0.48 (−2.77, 1.81)	Low	−0.48 (−2.77, 1.81)	Low
Topiramate – Aripiprazole	NA	–	−0.06 (−2.33, 2.18)	Low	−0.06 (−2.33, 2.18)	Low
Ziprasidone – Aripiprazole	NA	–	−0.40 (−2.31, 1.50)	Low	−0.40 (−2.31, 1.50)	Low
Fluvoxamine – Duloxetine	NA	–	1.28 (−1.31, 3.86)	Low	1.28 (−1.31, 3.86)	Low
GinkgoBiloba – Duloxetine	NA	–	1.30 (−1.31, 3.91)	Low	1.30 (−1.31, 3.91)	Low
Glycine – Duloxetine	NA	–	1.58 (−1.05, 4.18)	Low	1.58 (−1.05, 4.18)	Low
Haloperidol – Duloxetine	NA	–	1.27 (−1.59, 4.19)	Low	1.27 (−1.59, 4.19)	Low
Lamotrigine – Duloxetine	NA	–	1.16 (−0.95, 3.27)	Low	1.16 (−0.95, 3.27)	Low
Memantine – Duloxetine	NA	–	−0.61 (−3.25, 2.05)	Low	−0.61 (−3.25, 2.05)	Low
Minocycline – Duloxetine	NA	–	0.95 (−1.66, 3.56)	Low	0.95 (−1.66, 3.56)	Low
Mirtazapine – Duloxetine	NA	–	−3.69 (−6.80, −0.61)	Low	−3.69 (−6.80, −0.61)	Low
NaBenzoate – Duloxetine	NA	–	0.72 (−1.90, 3.33)	Low	0.72 (−1.90, 3.33)	Low
Pimozide – Duloxetine	NA	–	2.19 (−0.04, 4.50)	Moderate	2.19 (−0.04, 4.50)	Moderate
Placebo – Duloxetine	1.49 (−0.33, 3.34)	High	NE	–	1.49 (−0.33, 3.34)	High
Quetiapine – Duloxetine	NA	–	1.59 (−1.24, 4.40)	Low	1.59 (−1.24, 4.40)	Low
Risperidone – Duloxetine	NA	–	1.07 (−0.90, 3.06)	Low	1.07 (−0.90, 3.06)	Low
Sarcosine – Duloxetine	NA	–	1.26 (−1.36, 3.94)	Low	1.26 (−1.36, 3.94)	Low
Sulpiride – Duloxetine	NA	–	0.67 (−1.94, 3.29)	Low	0.67 (−1.94, 3.29)	Low
Topiramate – Duloxetine	NA	–	1.07 (−1.52, 3.68)	Low	1.07 (−1.52, 3.68)	Low

Table 4. Continued 1

Comparison	Direct evidence		Indirect evidence		Network meta-analysis	
	Mean diff (95% CI)	Quality of evidence	Mean diff (95% CrI)	Quality of evidence	Mean diff (95% CrI)	Quality of evidence
Ziprasidone – Duloxetine	NA	–	0.74 (−1.55, 3.08)	Low	0.74 (−1.55, 3.08)	Low
GinkgoBiloba–Fluvoxamine	NA	–	0.01 (−2.56, 2.61)	Low	0.01 (−2.56, 2.61)	Low
Glycine – Fluvoxamine	NA	–	0.29 (−2.31, 2.90)	Low	0.29 (−2.31, 2.90)	Low
Haloperidol – Fluvoxamine	NA	–	0.00 (−2.90, 2.89)	Low	0.00 (−2.90, 2.89)	Low
Lamotrigine – Fluvoxamine	NA	–	−0.12 (−2.23, 2.02)	Low	−0.12 (−2.23, 2.02)	Low
Memantine – Fluvoxamine	NA	–	−1.90 (−4.54, 0.76)	Moderate	−1.90 (−4.54, 0.76)	Moderate
Minocycline – Fluvoxamine	NA	–	−0.34 (−2.92, 2.27)	Low	−0.34 (−2.92, 2.27)	Low
Mirtazapine – Fluvoxamine	NA	–	−4.97 (−8.05, −1.86)	Low	−4.97 (−8.05, −1.86)	Low
NaBenzoate – Fluvoxamine	NA	–	−0.56 (−3.17, 2.07)	Low	−0.56 (−3.17, 2.07)	Low
Pimozide – Fluvoxamine	NA	–	0.92 (−1.32, 3.19)	Low	0.92 (−1.32, 3.19)	Low
Placebo – Fluvoxamine	0.21 (−1.63, 2.06)	Moderate	NE	–	0.21 (−1.63, 2.06)	Moderate
Quetiapine – Fluvoxamine	NA	–	0.31 (−2.51, 3.12)	Low	0.31 (−2.51, 3.12)	Low
Risperidone – Fluvoxamine	NA	–	−0.20 (−2.18, 1.78)	Very low	−0.20 (−2.18, 1.78)	Very low
Sarcosine – Fluvoxamine	NA	–	−0.01 (−2.64, 2.59)	Low	−0.01 (−2.64, 2.59)	Low
Sulpiride – Fluvoxamine	NA	–	−0.61 (−3.21, 2.01)	Low	−0.61 (−3.21, 2.01)	Low
Topiramate – Fluvoxamine	NA	–	−0.20 (−2.83, 2.41)	Low	−0.20 (−2.83, 2.41)	Low
Ziprasidone – Fluvoxamine	NA	–	−0.52 (−2.85, 1.78)	Low	−0.52 (−2.85, 1.78)	Low
Glycine – GinkgoBiloba	NA	–	0.27 (−2.31, 2.89)	Low	0.27 (−2.31, 2.89)	Low
Haloperidol – GinkgoBiloba	NA	–	−0.02 (−2.93, 2.91)	Low	−0.02 (−2.93, 2.91)	Low
Lamotrigine – GinkgoBiloba	NA	–	−0.13 (−2.25, 1.98)	Low	−0.13 (−2.25, 1.98)	Low
Memantine – GinkgoBiloba	NA	–	−1.90 (−4.56, 0.76)	Low	−1.90 (−4.56, 0.76)	Low
Minocycline – GinkgoBiloba	NA	–	−0.35 (−2.94, 2.24)	Very low	−0.35 (−2.94, 2.24)	Very low
Mirtazapine – GinkgoBiloba	NA	–	−4.99 (−8.10, −1.87)	Low	−4.99 (−8.10, −1.87)	Low
NaBenzoate – GinkgoBiloba	NA	–	−0.57 (−3.18, 2.05)	Low	−0.57 (−3.18, 2.05)	Low
Pimozide – GinkgoBiloba	NA	–	0.91 (−1.35, 3.16)	Very low	0.91 (−1.35, 3.16)	Very low
Placebo – GinkgoBiloba	0.20 (−1.63, 2.04)	Low	NE	–	0.20 (−1.63, 2.04)	Low
Quetiapine – GinkgoBiloba	NA	–	0.29 (−2.53, 3.11)	Low	0.29 (−2.53, 3.11)	Low
Risperidone – GinkgoBiloba	NA	–	−0.22 (−2.23, 1.78)	Very low	−0.22 (−2.23, 1.78)	Very low
Sarcosine – GinkgoBiloba	NA	–	−0.03 (−2.68, 2.59)	Low	−0.03 (−2.68, 2.59)	Low
Sulpiride – GinkgoBiloba	NA	–	−0.62 (−3.24, 1.97)	Low	−0.62 (−3.24, 1.97)	Low
Topiramate – GinkgoBiloba	NA	–	−0.22 (−2.81, 2.36)	Very low	−0.22 (−2.81, 2.36)	Very low
Ziprasidone – GinkgoBiloba	NA	–	−0.53 (−2.83, 1.75)	Low	−0.53 (−2.83, 1.75)	Low
Haloperidol – Glycine	NA	–	−0.29 (−3.21, 2.62)	Low	−0.29 (−3.21, 2.62)	Low
Lamotrigine – Glycine	NA	–	−0.41 (−2.52, 1.73)	Low	−0.41 (−2.52, 1.73)	Low
Memantine – Glycine	NA	–	−2.18 (−4.85, 0.48)	Low	−2.18 (−4.85, 0.48)	Low
Minocycline – Glycine	NA	–	−0.63 (−3.21, 1.98)	Low	−0.63 (−3.21, 1.98)	Low
Mirtazapine – Glycine	NA	–	−5.27 (−8.31, −2.15)	Low	−5.27 (−8.31, −2.15)	Low
NaBenzoate – Glycine	NA	–	−0.85 (−3.48, 1.75)	Low	−0.85 (−3.48, 1.75)	Low
Pimozide – Glycine	NA	–	0.62 (−1.62, 2.92)	Low	0.62 (−1.62, 2.92)	Low
Placebo – Glycine	−0.07 (−1.89, 1.78)	Moderate	NE	–	−0.07 (−1.89, 1.78)	Moderate
Quetiapine – Glycine	NA	–	0.02 (−2.85, 2.82)	Low	0.02 (−2.85, 2.82)	Low
Risperidone – Glycine	NA	–	−0.49 (−2.49, 1.52)	Low	−0.49 (−2.49, 1.52)	Low
Sarcosine – Glycine	NA	–	−0.30 (−2.95, 2.32)	Low	−0.30 (−2.95, 2.32)	Low
Sulpiride – Glycine	NA	–	−0.90 (−3.49, 1.73)	Low	−0.90 (−3.49, 1.73)	Low
Topiramate – Glycine	NA	–	−0.49 (−3.10, 2.12)	Low	−0.49 (−3.10, 2.12)	Low
Ziprasidone – Glycine	NA	–	−0.82 (−3.14, 1.49)	Low	−0.82 (−3.14, 1.49)	Low
Lamotrigine – Haloperidol	NA	–	−0.11 (−2.60, 2.37)	Low	−0.11 (−2.60, 2.37)	Low
Memantine – Haloperidol	NA	–	−1.88 (−4.86, 1.10)	Low	−1.88 (−4.86, 1.10)	Low
Minocycline – Haloperidol	NA	–	−0.33 (−3.23, 2.60)	Low	−0.33 (−3.23, 2.60)	Low
Mirtazapine – Haloperidol	NA	–	−4.96 (−8.33, −1.59)	Low	−4.96 (−8.33, −1.59)	Low
NaBenzoate – Haloperidol	NA	–	−0.56 (−3.50, 2.36)	Low	−0.56 (−3.50, 2.36)	Low
Pimozide – Haloperidol	NA	–	0.92 (−1.67, 3.54)	Low	0.92 (−1.67, 3.54)	Low
Placebo – Haloperidol	NA	–	0.22 (−2.04, 2.46)	Low	0.22 (−2.04, 2.46)	Low

Table 4. Continued 2

Comparison	Direct evidence		Indirect evidence		Network meta-analysis	
	Mean diff (95% CI)	Quality of evidence	Mean diff (95% CrI)	Quality of evidence	Mean diff (95% CrI)	Quality of evidence
Quetiapine – Haloperidol	NA	–	0.31 (−2.83, 3.41)	Low	0.31 (−2.83, 3.41)	Low
Risperidone – Haloperidol	NA	–	−0.19 (−2.60, 2.16)	Very low	−0.19 (−2.60, 2.16)	Very low
Sarcosine – Haloperidol	NA	–	−0.01 (−2.93, 2.89)	Low	−0.01 (−2.93, 2.89)	Low
Sulpiride – Haloperidol	NA	–	−0.60 (−3.54, 2.33)	Low	−0.60 (−3.54, 2.33)	Low
Topiramate – Haloperidol	NA	–	−0.19 (−3.15, 2.69)	Low	−0.19 (−3.15, 2.69)	Low
Ziprasidone – Haloperidol	NA	–	−0.52 (−3.19, 2.11)	Low	−0.52 (−3.19, 2.11)	Low
Memantine – Lamotrigine	NA	–	−1.77 (−3.96, 0.43)	Low	−1.77 (−3.96, 0.43)	Low
Minocycline – Lamotrigine	NA	–	−0.21 (−2.34, 1.90)	Low	−0.21 (−2.34, 1.90)	Low
Mirtazapine – Lamotrigine	NA	–	−4.85 (−7.52, −2.13)	Low	−4.85 (−7.52, −2.13)	Low
NaBenzoate – Lamotrigine	NA	–	−0.44 (−2.58, 1.71)	Low	−0.44 (−2.58, 1.71)	Low
Pimozide – Lamotrigine	NA	–	1.03 (−0.63, 2.75)	Very low	1.03 (−0.63, 2.75)	Very low
Placebo – Lamotrigine	0.33 (−0.73, 1.39)	Moderate	NE	–	0.33 (−0.73, 1.39)	Moderate
Quetiapine – Lamotrigine	NA	–	0.43 (−2.01, 2.82)	Low	0.43 (−2.01, 2.82)	Low
Risperidone – Lamotrigine	NA	–	−0.08 (−1.40, 1.22)	Very low	−0.08 (−1.40, 1.22)	Very low
Sarcosine – Lamotrigine	NA	–	0.10 (−2.05, 2.27)	Low	0.10 (−2.05, 2.27)	Low
Sulpiride – Lamotrigine	NA	–	−0.48 (−2.63, 1.64)	Low	−0.48 (−2.63, 1.64)	Low
Topiramate – Lamotrigine	NA	–	−0.08 (−2.24, 2.03)	Low	−0.08 (−2.24, 2.03)	Low
Ziprasidone – Lamotrigine	NA	–	−0.41 (−2.17, 1.34)	Low	−0.41 (−2.17, 1.34)	Low
Minocycline – Memantine	NA	–	1.55 (−1.09, 4.21)	Low	1.55 (−1.09, 4.21)	Low
Mirtazapine – Memantine	NA	–	−3.08 (−6.24, 0.05)	Very low	−3.08 (−6.24, 0.05)	Very low
NaBenzoate – Memantine	NA	–	1.32 (−1.36, 4.01)	Low	1.32 (−1.36, 4.01)	Low
Pimozide – Memantine	NA	–	2.81 (0.49, 5.16)	Very low	2.81 (0.49, 5.16)	Very low
Placebo – Memantine	2.10 (0.18, 4.03)	Moderate	NE	–	2.10 (0.18, 4.03)	Moderate
Quetiapine – Memantine	NA	–	2.20 (−0.71, 5.10)	Low	2.20 (−0.71, 5.10)	Low
Risperidone – Memantine	NA	–	1.68 (−0.39, 3.79)	Low	1.68 (−0.39, 3.79)	Low
Sarcosine – Memantine	NA	–	1.87 (−0.81, 4.51)	Low	1.87 (−0.81, 4.51)	Low
Sulpiride – Memantine	NA	–	1.28 (−1.42, 3.94)	Low	1.28 (−1.42, 3.94)	Low
Topiramate – Memantine	NA	–	1.68 (−0.98, 4.32)	Low	1.68 (−0.98, 4.32)	Low
Ziprasidone – Memantine	NA	–	1.36 (−1.00, 3.73)	Low	1.36 (−1.00, 3.73)	Low
Mirtazapine – Minocycline	NA	–	−4.64 (−7.71, −1.52)	Low	−4.64 (−7.71, −1.52)	Low
NaBenzoate – Minocycline	NA	–	−0.23 (−2.82, 2.38)	Low	−0.23 (−2.82, 2.38)	Low
Pimozide – Minocycline	NA	–	1.25 (−0.98, 3.51)	Low	1.25 (−0.98, 3.51)	Low
Placebo – Minocycline	0.54 (−1.27, 2.39)	Moderate	NE	–	0.54 (−1.27, 2.39)	Moderate
Quetiapine – Minocycline	NA	–	0.64 (−2.20, 3.49)	Low	0.64 (−2.20, 3.49)	Low
Risperidone – Minocycline	NA	–	0.12 (−1.86, 2.13)	Very low	0.12 (−1.86, 2.13)	Very low
Sarcosine – Minocycline	NA	–	0.31 (−2.33, 2.96)	Low	0.31 (−2.33, 2.96)	Low
Sulpiride – Minocycline	NA	–	−0.28 (−2.85, 2.32)	Low	−0.28 (−2.85, 2.32)	Low
Topiramate – Minocycline	NA	–	0.12 (−2.49, 2.72)	Low	0.12 (−2.49, 2.72)	Low
Ziprasidone – Minocycline	NA	–	−0.20 (−2.53, 2.12)	Low	−0.20 (−2.53, 2.12)	Low
NaBenzoate – Mirtazapine	NA	–	4.42 (1.27, 7.47)	Low	4.42 (1.27, 7.47)	Low
Pimozide – Mirtazapine	NA	–	5.89 (3.08, 8.72)	Moderate	5.89 (3.08, 8.72)	Moderate
Placebo – Mirtazapine	5.19 (2.69, 7.66)	Moderate	NE	–	5.19 (2.69, 7.66)	Moderate
Quetiapine – Mirtazapine	NA	–	5.28 (1.96, 8.57)	Moderate	5.28 (1.96, 8.57)	Moderate
Risperidone – Mirtazapine	NA	–	4.76 (2.14, 7.35)	Low	4.76 (2.14, 7.35)	Low
Sarcosine – Mirtazapine	NA	–	4.96 (1.82, 8.08)	Moderate	4.96 (1.82, 8.08)	Moderate
Sulpiride – Mirtazapine	NA	–	4.36 (1.23, 7.42)	Low	4.36 (1.23, 7.42)	Low
Topiramate – Mirtazapine	NA	–	4.77 (1.65, 7.82)	Low	4.77 (1.65, 7.82)	Low
Ziprasidone – Mirtazapine	NA	–	4.44 (1.58, 7.26)	Moderate	4.44 (1.58, 7.26)	Moderate
Pimozide – NaBenzoate	NA	–	1.48 (−0.781, 3.75)	Low	1.48 (−0.781, 3.75)	Low
Placebo – NaBenzoate	0.78 (−1.07, 2.62)	Low	NE	–	0.78 (−1.07, 2.62)	Low
Quetiapine – NaBenzoate	NA	–	0.87 (−2.02, 3.71)	Low	0.87 (−2.02, 3.71)	Low
Risperidone – NaBenzoate	NA	–	0.35 (−1.68, 2.34)	Very low	0.35 (−1.68, 2.34)	Very low
Sarcosine – NaBenzoate	NA	–	0.54 (−2.10, 3.16)	Low	0.54 (−2.10, 3.16)	Low

Table 4. Continued 3

Comparison	Direct evidence		Indirect evidence		Network meta-analysis	
	Mean diff (95% CI)	Quality of evidence	Mean diff (95% CrI)	Quality of evidence	Mean diff (95% CrI)	Quality of evidence
Sulpiride – NaBenzoate	NA	–	−0.05 (−2.67, 2.57)	Low	−0.05 (−2.67, 2.57)	Low
Topiramate – NaBenzoate	NA	–	0.36 (−2.27, 2.99)	Low	0.36 (−2.27, 2.99)	Low
Ziprasidone – NaBenzoate	NA	–	0.02 (−2.30, 2.346)	Low	0.02 (−2.30, 2.346)	Low
Placebo – Pimozide	−0.70 (−2.03, 0.60)	Moderate	NE	–	−0.70 (−2.03, 0.60)	Moderate
Quetiapine – Pimozide	NA	–	−0.60 (−3.20, 1.91)	Low	−0.60 (−3.20, 1.91)	Low
Risperidone – Pimozide	NA	–	−1.13 (−2.67, 0.40)	Very low	−1.13 (−2.67, 0.40)	Very low
Sarcosine – Pimozide	NA	–	−0.94 (−3.24, 1.35)	Low	−0.94 (−3.24, 1.35)	Low
Sulpiride – Pimozide	NA	–	−1.53 (−3.81, 0.74)	Low	−1.53 (−3.81, 0.74)	Low
Topiramate – Pimozide	NA	–	−1.13 (−3.42, 1.14)	Very low	−1.13 (−3.42, 1.14)	Very low
Ziprasidone – Pimozide	NA	–	−1.45 (−3.38, 0.44)	Low	−1.45 (−3.38, 0.44)	Low
Quetiapine – Placebo	NA	–	0.09 (−2.09, 2.27)	Low	0.09 (−2.09, 2.27)	Low
Risperidone – Placebo	−0.29 (−1.1, 0.54)	Low	−1.8 (−4.3, 0.84)	Very low	−0.42 (−1.21, 0.35)	Low
Sarcosine – Placebo	−0.23 (−2.11, 1.63)	Moderate	NE	–	−0.23 (−2.11, 1.63)	Moderate
Sulpiride – Placebo	−0.83 (−2.69, 1.01)	Moderate	NE	–	−0.83 (−2.69, 1.01)	Moderate
Topiramate – Placebo	−0.42 (−2.26, 1.41)	Low	NE	–	−0.42 (−2.26, 1.41)	Low
Ziprasidone – Placebo	−0.74 (−2.13, 0.64)	Moderate	−0.07 (−1.9, 2.1)	Low	−0.74 (−2.13, 0.64)	Moderate
Risperidone – Quetiapine	NA	–	−0.51 (−2.83, 1.78)	Low	−0.51 (−2.83, 1.78)	Low
Sarcosine – Quetiapine	NA	–	−0.32 (−3.16, 2.52)	Low	−0.32 (−3.16, 2.52)	Low
Sulpiride – Quetiapine	NA	–	−0.92 (−3.77, 1.97)	Low	−0.92 (−3.77, 1.97)	Low
Topiramate – Quetiapine	NA	–	−0.52 (−3.41, 2.36)	Low	−0.52 (−3.41, 2.36)	Low
Ziprasidone – Quetiapine	NA	–	−0.84 (−3.41, 1.73)	Low	−0.84 (−3.41, 1.73)	Low
Sarcosine – Risperidone	NA	–	0.18 (−1.86, 2.22)	Low	0.18 (−1.86, 2.22)	Low
Sulpiride – Risperidone	NA	–	−0.40 (−2.41, 1.60)	Low	−0.40 (−2.41, 1.60)	Low
Topiramate – Risperidone	NA	–	0.00 (−2.01, 2.00)	Very low	0.00 (−2.01, 2.00)	Very low
Ziprasidone – Risperidone	0.36 (−1.5, 2.2)	Low	−1.1 (−3.1, 0.91)	Very low	−0.33 (−1.70, 1.07)	Low
Sulpiride – Sarcosine	NA	–	−0.59 (−3.22, 2.05)	Low	−0.59 (−3.22, 2.05)	Low
Topiramate – Sarcosine	NA	–	−0.18 (−2.85, 2.46)	Low	−0.18 (−2.85, 2.46)	Low
Ziprasidone – Sarcosine	NA	–	−0.51 (−2.87, 1.83)	Low	−0.51 (−2.87, 1.83)	Low
Topiramate – Sulpiride	NA	–	0.40 (−2.19, 3.05)	Low	0.40 (−2.19, 3.05)	Low
Ziprasidone – Sulpiride	NA	–	0.08 (−2.23, 2.40)	Low	0.08 (−2.23, 2.40)	Low
Ziprasidone – Topiramate	NA	–	−0.32 (−2.62, 2.00)	Low	−0.32 (−2.62, 2.00)	Low

CI, confidence interval; CrI, credible intervals; NE, not estimable; NA, not applicable.

Table 5. NMA results sorted based on GRADE certainty of evidence for the comparisons of active augmentation strategies versus placebo for Schizophrenia refractory/partially responding to clozapine

Outcome	Certainty of evidence	Classification	Intervention	MD (95% CrI)
Reduction in PANSS/BPRS	High (high and moderate)	Amongst the most effective	Mirtazapine	−5.2 (−7.7, −2.7)
			Memantine	−2.1 (−4.0, −0.19)
		Amongst the least effective	Glycine	−0.07 (−1.89, 1.78)
	Low (low and very low)	May be more effective than placebo	None	

NMA, network meta-analysis; PANSS, positive and negative syndrome scale; BPRS, brief psychiatric rating scale; CI, confidence interval; CrI, credible intervals; MD, mean difference.

using a frequentist approach which does not provide ample flexibility in analysis. Markov Chain Monte Carlo simulations used in Bayesian analysis allow realistic models to be fitted in complex datasets. It gives a more principled way of easily combining prior knowledge with available data within the realm of a solid decision and theoretical framework, which is not possible with a frequentist approach. Secondly, our NMA includes certainty of the evidence for the comparisons between the treatment, which would help in building confidence in the therapeutic

agent.

The demographics of the patients included in our network meta-analysis were like a meta-analysis conducted on ultra-resistant patients [56]. Tiihonen *et al.* [57] conducted a meta-analysis including four studies comparing lamotrigine with a placebo and found lamotrigine has higher efficacy than a placebo in clozapine-resistant schizophrenia. However, on further exploring the articles included in this meta-analysis, the inclusion does not seem to be restricted to clozapine resistance. The review authors have focussed on an add-on lamotrigine therapy but they have included studies with patients on other conventional and atypical antipsychotics apart from clozapine. This may be the reason for contradicting findings between this meta-analysis and this NMA showing contrasting results as our NMA concludes NMA, as our results conclude lamotrigine to be no better than placebo. Similarly, a pairwise meta-analysis by Siskind *et al.* [58] showed interventions like aripiprazole, fluoxetine, and sodium valproate to be most effective, but the inclusion criteria were not confined according to response to clozapine i.e., patients receiving clozapine for the first time were included along with partial responders and clozapine refractory patients. This meta-analysis did not confine inclusion criteria to patients with schizophrenia but in addition included schizoaffective disorder and psychosis spectrum disorders as well. In addition, the two studies mentioned above are pairwise meta-analyses whereas our study is a network meta-analysis that ranks treatments based on their SUCRA scores along with the calculation of the relative effect of each intervention tested against all others.

The inclusion of more severe patients in medication trials and the increased likelihood of bias in psychotherapy research were the two main differences discovered between the two categories of studies according to a report by Bighelli *et al.* [59]. These variations suggest that before considering a network meta-analysis, study and patient characteristics should be carefully taken into account. Thus, we did not include psychological interventions in this analysis.

In our NMA, ranking results and relative effects estimates indicate towards same pharmacological agents for improvement in symptoms in comparison to placebo. This allows us to interpret results with more confidence. Furthermore, there was coherence between the direct and indirect evidence synthesized in this NMA, thus fulfilling the criteria of transitivity assumption.

There are certain limitations to this analysis. Safety reporting equipment was different across the studies, and thus we could not do a quantitative analysis of the safety data. Second, the number of studies per comparison is limited to one for most of the comparisons, and the number of participants per study is very small for most of the studies. However, using the Bayesian approach using non-informative priors in this situation makes the interpretation of results reliable and straightforward, which is the main strength of our study.

In conclusion, our findings indicate that mirtazapine and memantine are the two best augmentation agents in schizophrenia patients who are partial/non-responders to clozapine therapy. However, studies with large sample sizes are warranted to enhance the generalizability of the findings.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Literature search: Archana Mishra. Study screening and selection: Archana Mishra, Rituparna Maiti, Biswa Ranjan Mishra, Anand Srinivasan. Data extraction and management: Archana Mishra, Rituparna Maiti, Biswa Ranjan Mishra, Anand Srinivasan. Data analysis and interpretation of data: Archana Mishra. Drafting of the manuscript: Archana Mishra, Rituparna Maiti. Concept and design: Rituparna Maiti, Anand Srinivasan. Critical revision of the manuscript for important intellectual content: Biswa Ranjan Mishra, Anand Srinivasan. Final approval of the manuscript: Archana Mishra, Rituparna Maiti, Biswa Ranjan Mishra, Anand Srinivasan.

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