Pharmacological and nonpharmacological augmentation treatments for clozapine-resistant schizophrenia: a systematic review and network meta-analysis with normalized entropy assessment

1. Introduction

Clozapine is the treatment of choice for the management of treatment-resistant schizophrenia (TRS) (Warnez and Alessi-Severini, 2014). However, more than half of patients with TRS did not respond to clozapine, and clozapine-resistant schizophrenia (CRS) has been suggested as a condition for those with TRS who failed to respond to an adequate trial of clozapine (Howes et al., 2017, Warnez and Alessi-Severini, 2014). Previous reviews suggested that adding aripiprazole, fluoxetine, and valproate might be superior to placebo for patients with CRS (Siskind et al., 2018); however, the authors concluded that these findings were tempered, because the majority of the studies were judged as having uncertain quality (Siskind et al., 2018). Nonpharmacological interventions for CRS have also been evaluated, such as electroconvulsive therapy (ECT) (Petrides et al., 2015, Purohith et al., 2022), repetitive transcranial magnetic stimulation (rTMS) (Wagner et al., 2019), and cognitive-behavioral therapy (CBT) (Barretto et al., 2009). Although moderate-quality evidence has suggested that ECT has positive effects on patients with TRS compared to standard care (Sinclair et al., 2019), evidence is still insufficient to validate the benefits of ECT for patients with CRS. A recent meta-analysis examining the efficacy of ECT for CRS reported that combining ECT with clozapine was superior to clozapine monotherapy in treating overall symptoms among patients with CRS (Wang et al., 2018); however, 17 of the 18 included studies had poor quality.

To date, few head-to-head RCT comparisons have been conducted on the different pharmacological and nonpharmacological interventions for the treatment of CRS. A recent expert consensus-based treatment strategy recommendation advocated different interventions for overall, positive, and negative symptoms (Wagner et al., 2020), because the positive and negative symptoms may respond differentially to the same intervention.

The aim of the current study was to comprehensively integrate all available evidence from randomized controlled trials (RCTs) on augmentation treatment for CRS by conducting network meta-analysis (NMA). A better understanding of the relative efficacy and acceptability of these treatments is essential for informed decision making in this difficult-to-treat population. Moreover, the findings of our NMA may provide evidence-based information to guide clinical practice and future RCTs.

2. Methods and materials

The current systematic review and NMA was registered in PROSPERO (CRD42021262197) (eAppendix 1 in the Supplement) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement (eAppendix 2) and the A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR2) (eAppendix 3).

2.1. Search strategy and selection criteria

From inception to July 10th, 2021, two authors (TCY and FCY) independently searched the MEDLINE, PubMed, EMBASE, Cochrane Library, Clinical trial registry (including ClinicalTrial.gov and other International Clinical Trials Registry Platform (ICTRP)), and PsycINFO databases (eAppendix 4). The PICO (population, intervention, comparison, outcome) settings were: (1) P: patients with schizophrenia who failed to respond to clozapine; (2) I: augmentation treatment (e.g., medication, oral supplementation, ECT, CBT); (3) C: placebo, active control, or treatment-as-usual; and (4) O: the change in overall, positive, and negative symptoms of schizophrenia. We only included placebo-controlled and head-to-head RCTs. We excluded studies if they did not indicate “resistant to clozapine”, “refractory to clozapine”, “nonresponse to clozapine”, or “partial response to clozapine”. We excluded studies using clozapine at a dose of < 300 mg/day, as this is likely to be a suboptimal dosage for the treatment of refractory schizophrenia (Subramanian et al., 2017). In order to satisfy a transitivity assumption of NMA, we excluded studies if patients with CRS were treated with clozapine and other active treatment(s) before adding an augmentation treatment. For example, we did not include the study by Morrison and colleague (Morrison et al., 2018) who compared CBT with treatment as usual for patients with CRS, because 242/487 patients had been treated with antidepressants. Two authors (MHC and PTT) independently evaluated the risk of bias of recruited studies with the Version 2 of the Cochrane tool for assessing risk of bias (ROB 2) (Sterne et al., 2019).

2.2. Data extraction

Study selection and data extraction were performed independently by two authors (TCY and FCY). The primary outcome was the mean change from baseline to end point in overall symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS), or any other validated scale for the assessment of overall schizophrenia symptoms. Intention-to-treat data sets were used whenever available. Secondary outcomes were mean changes in positive and negative symptoms of schizophrenia and acceptability (all-cause discontinuation). Discrepancies or issues of study methodology and quality were resolved by consulting with the corresponding author (CSL).

2.3. Statistical analysis

Data analyses were conducted using R-Project (V.4.0.3, R Foundation) and STATA version 16.0 (StataCorp LLC Statistics/Data Analysis StataCorp, Texas, USA). We performed NMA in a frequentist setting. We used the random-effects model and assumed common heterogeneity across all comparisons. For continuous outcomes, the effect sizes were calculated as Hedges' g standardized mean differences (SMDs) with 95 % confidence intervals (CIs). We extracted the mean and standard deviation. If the studies presented data in other forms, these data were converted using the methods in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019) and the method reported by Higgins et al. (2008). For binary outcomes, the effect sizes were calculated as odds ratios (ORs) with 95 % CIs. Negative values of SMD in indicated an improvement in psychopathology of schizophrenia. For interpretation of SMD, we followed the rules of classifying < |0.2| as very small, |0.2|-|0.5| as small, |0.5|-|0.8| as moderate, and > |0.8|as large (Sullivan and Feinn, 2012). We ranked treatments using the surface under the cumulative ranking curve (SUCRA), which could be interpreted as the probability of being among the best option in the network. SUCRA ranges from 0 to 1; the greater the SUCRA value of a treatment, the better its performance is. Evidence has expressed concerns over the uncertainty of SUCRA-based ranking (Trinquart et al., 2016); therefore, we calculated normalized entropy to quantify the uncertainty of treatment ranking (Wu et al., 2021). Normalized entropy ranges between 0 and 1, and a lower value indicates greater certainty. If the SUCRA value of a treatment is associated with a large value of normalized entropy, the ranking of this treatment is more likely to be affected by minor modifications to the current evidence or the addition of new evidence.

We planned several meta-regression analyses in advance to assess the effect of potential moderators. If different instruments were used to measure the baseline symptoms of schizophrenia, the scores were converted to PANSS scores using the methods previously suggested (Thorlund et al., 2011). The transitivity assumption of our NMA was examined by the following three points: (1) using the design-by-treatment interaction model and nodesplitting method; (2) the differences in the efficacy of the placebo arm in pharmacological interventions versus the efficacy of the control arm in nonpharmacological interventions; (3) the distribution of the moderators across treatments and studies. Moreover, we examined the number of the moderators that were considered outliers by modified Z scores and Tukey methods for each study (Kolbaşi and Ünsal, 2019). Several statistical measures were performed to examine the potential outlying and influential studies in our NMA, including raw residuals, standardized residuals, studentized residuals, Mahalanobis distances, and leverage. The smallstudy effects were examined by comparison-adjusted funnel plots and Egger's tests. Sensitivity analyses were performed that excluded studies with high ROB or non-blinded RCTs. The p values for all comparisons were two-tailed, and a cut-off point of 0.05 was considered statistically significant.

3. Results

3.1. Study characteristics

We identified 35 RCTs including 24 augmentation treatments (23 active augmentation treatments and one placebo augmentation) through literature search. The 23 augmentation treatments

included 8 antipsychotics, 3 N-methyl D-aspartate (NMDA) receptor agonists, 3 antidepressants, 2 antiepileptics, 2 brain stimulation, 1 NDMA receptor antagonist (memantine), 1 alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor agonist (ampakine), Ginkgo biloba, minocycline, and CBT. The PRISMA flowchart is shown in Fig. 1 with the details of search strategy in the Supplement (eAppendix 4). These 35 RCTs spanned 1996–2019, and constituted a total of 1472 patients with CRS without major psychiatric comorbidities (eTable 1). These patients had a mean age of 37.30 years (standard deviation (SD) 4.67), a mean male proportion of 67.62 % (13.31 %), a mean illness duration of 188.34 (62.88) months, a mean PANSS total score at baseline of 76.19 (10.76), a mean daily clozapine dose of 440.80 (91.27) mg, and a mean clozapine treatment duration of 1168.22 (710.28) days. Details of the definition of CRS for each study are shown in Supplement (eTable 2).

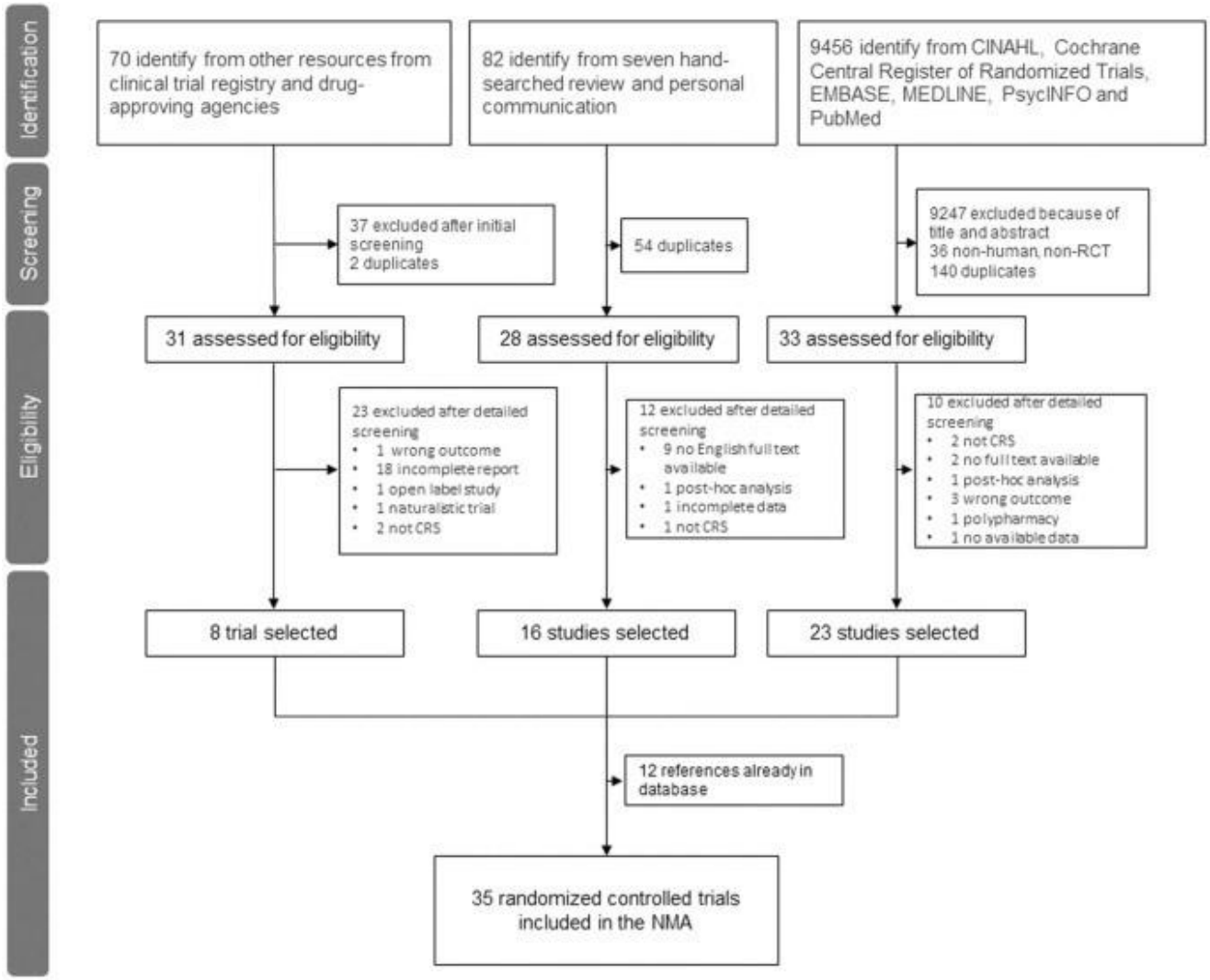

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Fig. 1. PRISMA flow chart.

3.2. Study quality

Among the 35 RCTs, four RCTs were considered to be of a high ROB for both primary and secondary outcomes (eFig. 1), with random sequence generation being the most frequent domain. The high ROB in each domain ranged from 0.0 % to 6.7 % (eFig. 2).

3.3. Primary outcomes

Fig. 2(A) presents the network plot for the primary outcome and demonstrates that risperidone (k = 6, n = 249) was the most common augmentation treatment for CRS, followed by aripiprazole (k = 3, n = 308). There were only two head-to-head studies (amisulpride versus quetiapine; risperidone versus ziprasidone). The network plots for the secondary outcomes are shown in the Supplement (eFig. 3).

Fig. 2(B) shows the NMA estimates of the augmentation treatments compared with placebo in overall symptoms. Mirtazapine (SMD: −4.41; 95 % CI: −5.61, −3.21), ECT (SMD: −4.32; 95 % CI: −5.43, −3.21), memantine (SMD: −2.02; 95 % CI: −3.14, −0.91), duloxetine (SMD: −1.27; 95 % CI: −2.34, −0.20), and rTMS (SMD: −0.90; 95 % CI: −1.69, −0.12) were superior to placebo/control.

Fig. 2(C) shows the comparisons between all augmentation interventions. Mirtazapine and ECT significantly reduced overall symptoms more than the other interventions, while the comparison between these two drugs was not significant. Memantine significantly reduced overall symptoms more than the other 15 interventions, while quetiapine significantly reduced overall symptoms less than the other seven interventions. Fig. 2(D) shows the treatment ranking by SUCRA and normalized entropy. Clearly, only mirtazapine, ECT, and memantine had higher SUCRA values and lower normalized entropy.

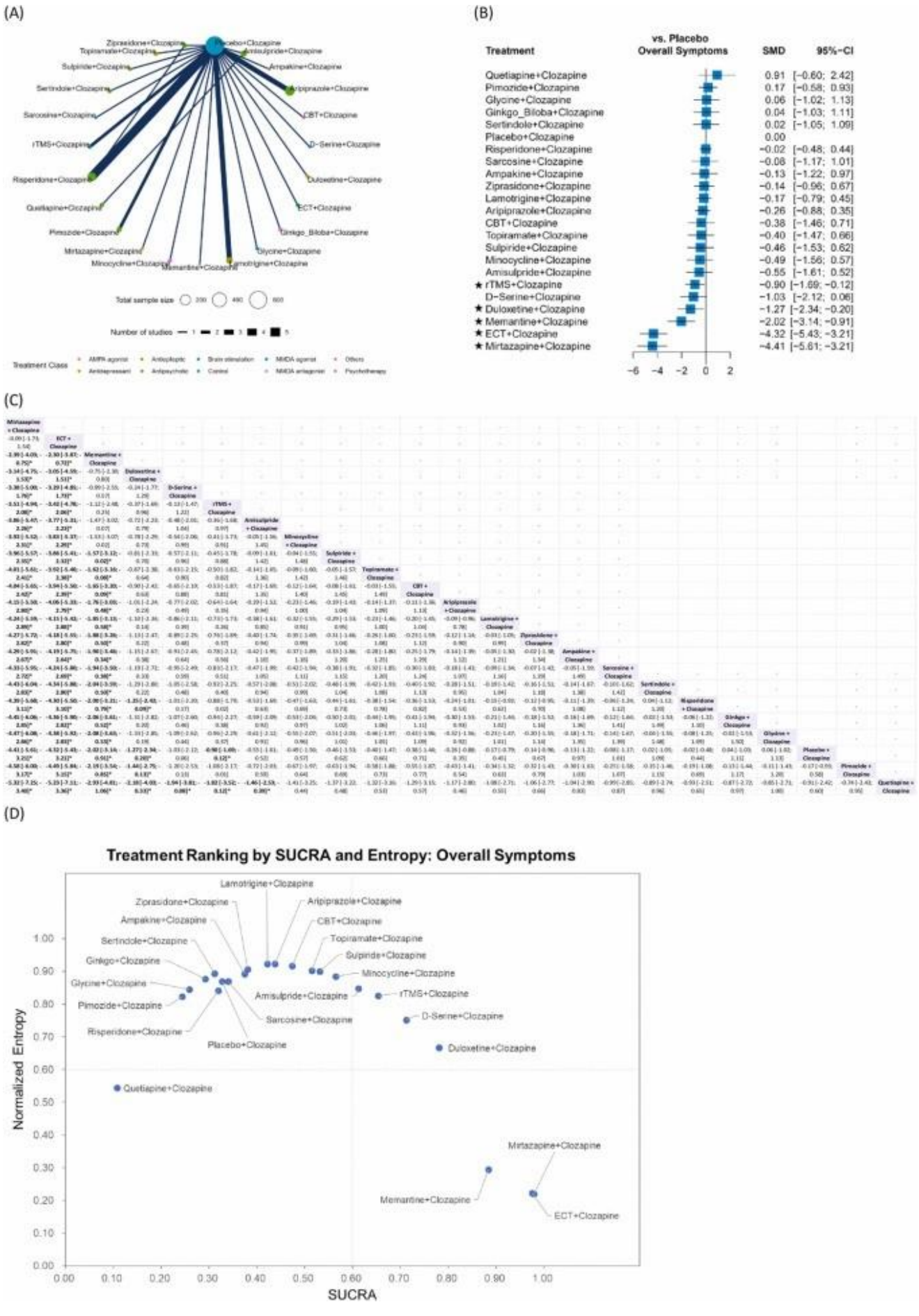

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Fig. 2. Relative efficacy and ranking for overall symptoms. (A) Network diagram for overall symptoms. Line width is proportional to the number of trials including every pair of treatments (direct comparisons). Circle size is proportional to the total number of patients for each treatment in the network. (B) Forest plots of network meta-analysis of all trials for overall symptoms. (C) League table of overall symptoms. Data are SMDs (95 % CrI) in the columndefining treatment compared with the row-defining treatment. Negative values favor the column-defining treatment (order by rank from high to low). (D) Treatment ranking by SUCRA and entropy: overall symptoms. *Abbreviation: CBT, cognitive behavioral treatment; CI, confidence interval; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; SMD, standardized mean difference; SUCRA, surface under the cumulative ranking curve.

3.4. Secondary outcomes

Only ECT (SMD: −5.18; 95 % CI: −5.86, −4.49) and memantine (SMD: −0.80; 95 % CI: −1.43, −0.16) were superior to placebo for positive symptoms [Fig. 3(A)]. Only memantine (SMD: −3.38; 95 % CI: −4.50, −2.26), duloxetine (SMD: −3.27; 95 % CI: −4.25, −2.29), and mirtazapine (SMD: −1.73; 95 % CI: −2.71, −0.74) were superior to placebo for negative symptoms [Fig. 3(B)]. Only amisulpride was superior to placebo (risk ratio: 0.21; 95 % CI: 0.05, 0.93) for acceptability [Fig. 3(C)].

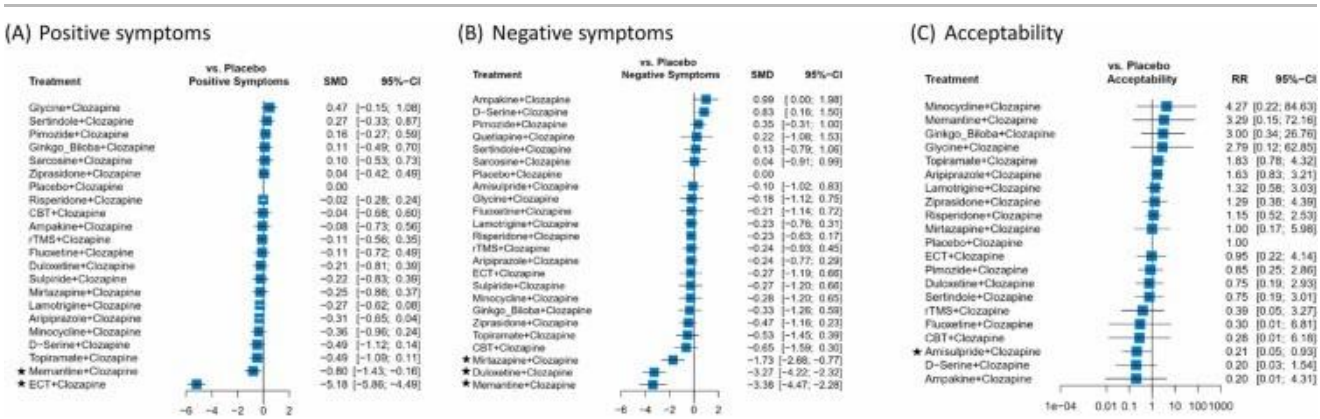

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Fig. 3. Forest plots of network meta-analysis of all trials for (A) positive symptoms, (B) negative symptoms and (C) acceptability. *statistical significance. †Treatments were compared with placebo, which was the reference. ‡Abbreviation: CBT, cognitive behavioral treatment; CI, confidence interval; ECT, electroconvulsive therapy; RR, risk ratio, rTMS, repetitive transcranial magnetic. stimulation.

The comparisons between active interventions for the secondary outcomes showed that ECT was superior to all of the other interventions for the positive symptoms (eFig. 4), and memantine significant reduced more positive symptoms than the other five interventions.

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Glycine was inferior to the other six interventions for positive symptoms. or negative symptoms (eFig. 5), memantine and duloxetine significantly attained greater reduction than the other 22 interventions, while the comparison between these two drugs was not statistically significant. Mirtazapine was superior to the other 19 interventions, and D-serine and ampakine were inferior to many of the other interventions over the negative symptoms. For acceptability (eFig. 6), all of the comparisons were not significant.

The treatment ranking based on the SUCRA value and normalized entropy (eFig. 7) showed that ECT had a higher SUCRA value and lower normalized entropy for the positive symptoms, while the normalized entropy for memantine was high. For negative symptoms (eFig. 8), memantine, duloxetine, and mirtazapine had higher SUCRA values and lower normalized entropy. For acceptability (eFig. 9), none of the interventions had higher SUCRA values with lower normalized entropy.

Fig. 4 shows all the values of the SUCRA and normalized entropy of the included augmentation treatments. An orange high positive slope indicates: (1) statistical significance on point estimates compared with the placebo; and (2) small normalized entropy with large SUCRA values. Importantly, all antipsychotics, antiepileptics, and N-methyl D-aspartate receptor agonists were not associated with more efficacy than placebo in the four domains.

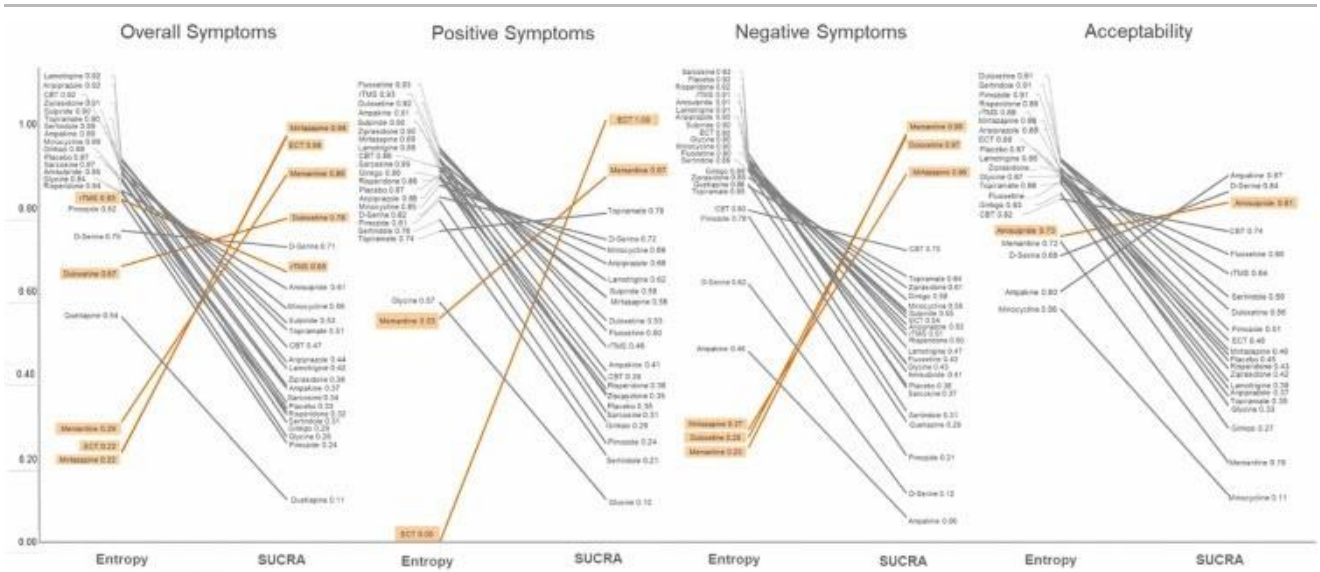

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Fig. 4. Slope graphs of normalized entropy and SUCRA values for all study outcomes. *Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; SUCRA, surface under the cumulative ranking curve. † Higher value of SURCA indicates better ranking, and lower value of normalized entropy indicates more certainty. ‡ Origin line indicates statistical significance on point estimate when compared with placebo.

3.5. Meta-regression and publication bias

We did not find any significant moderators (eTable 3), except for higher baseline PANSS scores having less efficacy in negative symptoms. Small-study effects were observed for positive and negative symptoms, but not for overall symptoms and acceptability (eFigure 10).

3.6. Transitivity assumption

We provide visual representations of the potential moderators in eFigure 11–eFigure 15. The number of outlying moderators in each study is shown in eTable 4. Only four studies had one outlier by modified Z score, and only one study had one outlier by Tukey method. The placebo responses were significant for the overall (SMD: −0.30; 95 % CI: −0.45, −0.13), positive (SMD: −0.23; 95 % CI: −0.36, −0.10), and negative (SMD: −0.23; 95 % CI: −0.36, −0.10) symptoms. The comparisons between pharmacological placebo and nonpharmacological placebo/control were not significant for overall, positive, and negative symptoms (eFigure 16–eFigure 18). The nodesplitting and design-by-treatment interaction models of the four study outcomes did not show any obvious evidence of inconsistency (eTable 5).

3.7. Potential outlying and influential study and sensitivity analysis

The measures for detecting a potential outlying and influential study showed that there was no potential influential study in the overall and positive symptoms (eTable 6 and eTable 7). We found one influential study for the negative symptoms (eTable 8), and this study used mirtazapine augmentation treatment (Zoccali et al., 2004). We found six influential studies for the outcome of acceptability (Buchanan et al., 1996, Goff et al., 2001, Muscatello et al., 2011, Nielsen et al., 2012, Petrides et al., 2015, Zoccali et al., 2004) (eTable 9); however, the augmentation treatments of these six studies were not associated with statistical significance compared to placebo. The sensitivity analyses, which excluded studies with high ROB and nonblinded RCTs, showed similar point estimates for all primary and secondary outcomes (eFigs. 19–26).

4. Discussion

The main findings were that: (1) mirtazapine, ECT, and memantine were ranked the best three augmentation treatments with less uncertainty for overall symptoms; (2) ECT was ranked the best with less uncertainty for positive symptoms; (3) memantine, duloxetine, and mirtazapine were ranked the best with less certainty for negative symptoms; (4) all antipsychotics, antiepileptics, and N-methyl D-aspartate receptor agonists were not associated with more efficacy than placebo in overall, positive, and negative symptoms.

The demographics of our participants were similar to a recent meta-analysis including 71 studies (n = 2731) with CRS (Campana et al., 2021), suggesting that our study participants were representative of CRS. In the current NMA, ECT was ranked as the second-best treatment with less uncertainty for overall symptoms (large effect size), and ranked as the best treatment with less certainty for positive symptoms (large effect size). The recent study also showed the benefits of maintenance ECT in CRS for improvement in the overall level of functioning and the severity of the illness and reduced hospital days (Purohith et al., 2022). owever, the efficacy of ECT for negative symptoms was not

superior to placebo for CRS. Future RCTs with large sample size are strongly encouraged to examine the efficacy of ECT for CRS.

Another interesting finding was that rTMS was superior to placebo in treating overall symptoms of CRS. A previous review article indicated that rTMS was superior to sham for medication-resistant auditory verbal hallucination, particularly applied at the left temporoparietal area with a frequency of 1 Hz (Slotema et al., 2014). However, this rTMS protocol was not superior to sham in treating other psychotic symptoms such as formal thought disorders and delusions (Slotema et al., 2014). The pathophysiology of schizophrenia has been associated with abnormalities in brain plasticity, possibly GABAergic interneurons mediating cortical inhibition (Radhu et al., 2013). The dysregulation of $GABA_B$-mediated inhibition (e.g., cortical silent period) could be improved after rTMS treatment (Daskalakis et al., 2007, Wang et al., 2022). Therefore, the benefits of rTMS on CRS might be associated with the synergic effects on cortical inhibition. However, the normalized entropy of rTMS is high in the current NMA, implying that the application of rTMS for CRS requires future investigation.

A recent expert-based augmentation strategy reached consensus for adding antidepressants for clozapine-refractory negative symptoms (Porcelli et al., 2012, Wagner et al., 2020). Our study provided supporting evidence for this recommendation. We found that augmentation with mirtazapine or duloxetine, but not fluoxetine, was superior to placebo in reducing negative symptoms of CRS. A previous meta-analytic study including 82 RCTs reported that antidepressant augmentation was superior to placebo in reducing overall, positive, and negative symptoms in patients with schizophrenia (Helfer et al., 2016). The individual class analysis found that duloxetine and mirtazapine had large effect sizes on negative symptoms, which were consistent with our findings. In the current NMA, the majority of the included studies (31/35) excluded patients with comorbid major depressive disorder and severe suicidal ideation; therefore, the efficacy of mirtazapine and duloxetine on negative symptoms of CRS might not be completely explained by the improvement of depressive symptoms overlapping with negative symptoms, such as anhedonia, emotional blunting, and anergia.

In contrast to earlier findings (Porcelli et al., 2012, Siskind et al., 2018, Taylor et al., 2012), current NMA did not detect any evidence for using antipsychotics in CRS treatment. Nonresponse to dopamine antagonists implies the importance of non-dopamine associated neurobiology in TRS and CRS (Demjaha et al., 2014, Demjaha et al., 2012, Kapur et al., 1999). This finding corroborates the results of recent works in functional magnetic resonance imaging, which demonstrated that glutamate hypofunction may be an important biological feature of treatment resistance to antipsychotics (Limongi et al., 2020, Ochi et al., 2022). Additionally, we found that memantine was associated with more efficacy than placebo in overall, positive, and negative symptoms. Previous studies have suggested that the efficacy of clozapine may rely on increasing the expression of NMDA and glutamate metabotropic receptors (de Lucena et al., 2009, Gray et al., 2009). However, a neuroimaging study reported that patients with CRS had lower glutamate level in the dorsolateral prefrontal cortex and putamen compared to patients with TRS or who were first-line treatment responders (Goldstein et al., 2015). This might explain why the memantine augmentation effect is only observed in CRS but not in TRS (Lieberman et al., 2009). The benefits of memantine on CRS need to be validated in future RCTs.

This study has several limitations. First, most of the comparisons between active interventions were derived from indirect comparisons, because few head-to-head studies were available. Second, the study using mirtazapine augmentation treatment was determined to be an influential study for the negative symptoms, and small-study effects were observed for positive and negative symptoms. Third, the prerequisite of failed treatment was referred to pharmacological treatments and there is no consensus of minimum requirement of nonpharmacological treatment to.

date. Fourth, there was only one study for ECT, memantine, and duloxetine, and the face validity might be limited. Therefore, we calculated the normalized entropy and suggested these three augmentation treatments might be with low uncertainty. Fifth, there are still several potential or unmeasured confounders in the enrolled studies which might have influenced the results, such as drug adherence or smoking status. For example, a small number of smokers were included in three studies (Anil Yağcioğlu et al., 2005; Kelly et al., 2015; Lane et al., 2006) which could possibly affect the efficacy of clozapine. Finally, we observe a clear placebo effect in the control group; therefore, the large effect size of ECT may be related to the study by Petrides et al. using treatment-as-usual instead of placebo as a comparator, which may increase the effect size of ECT (Petrides et al., 2015).

Patients with CRS inevitably come into contact with mental health services (Warnez and AlessiSeverini, 2014). We observed a small but significant placebo response in this difficult-to-treat population, and this strongly suggests that future RCTs with large sample size are necessary to examine and validate an efficacious augmentation for patients with CRS. In real-world settings, how these treatment augmentations work is challenging, because complex patients with CRS are often excluded from RCTs (e.g., high physical comorbidities or high suicide risk).
Our findings may be tentative and require validation by future large-scale RCTs.

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