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

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

Aims & Objectives
To integrate all evidence derived from randomized controlled trials (RCTs) of both pharmacological and nonpharmacological augmentation interventions for CRS.

Methods
Six major electronic databases were systematically searched for RCTs published until July 10, 2021. The primary outcome was change in overall symptoms, and the secondary outcomes were positive and negative symptoms and acceptability. We performed random-effects network meta-analysis. Normalized entropy was calculated to examine the uncertainty of treatment ranking.

Results
We identified 35 RCTs (1472 patients with 23 active augmentation treatments) with a mean daily clozapine dose of 440.80 (91.27) mg for 1168.22 (710.28) days. Network meta-analysis of overall symptoms (reported as standardized mean difference; 95% confidence interval) with consistent results indicated that mirtazapine (-4.41; -5.61, -3.21), electroconvulsive therapy (ECT) (-4.32; -5.43, -3.21), and memantine (-2.02; -3.14, -0.91) were ranked as the best three treatments. For positive symptoms, ECT (-5.18; -5.86, -4.49) was ranked the best with less uncertainty. For negative symptoms, memantine (-3.38; -4.50, -2.26), duloxetine (-3.27; -4.25, -2.29), and mirtazapine (-1.73; -2.71, -0.74) were ranked the best three treatments with less uncertainty. All antipsychotics, N-methyl d-aspartate receptor agonists, and antiepileptics were not associated with more efficacy than placebo. Compared to placebo, only amisulpride had statistically significant lower discontinuation rate (risk ratio: 0.21; 95% CI: 0.05, 0.93).

Discussion & Conclusion
Add-on mirtazapine, ECT, and memantine were the most efficacious augmentation options for CRS. Data on other important outcomes such as cognitive functioning or quality of life were rarely reported, making further large-scale, well-designed RCTs necessary.