Journal of Psychiatric Research 105 (2018) 23–32

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

ECT augmentation of clozapine for clozapine-resistant schizophrenia: A meta-analysis of randomized controlled trials

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ARTICLE INFO

Keywords:
ECT
Clozapine
Treatment-resistant
Schizophrenia
Memory
Headache
Response
Remission

ABSTRACT

Treatment-resistant schizophrenia (TRS) is common and debilitating. A subgroup of patients even has clozapine-resistant schizophrenia (CRS). We aimed to evaluate the efficacy and safety of electroconvulsive therapy (ECT) augmentation of clozapine for CRS. Systematic literature search of randomized controlled trials (RCTs) reporting on ECT augmentation of clozapine in CRS. Co-primary outcomes included symptomatic improvement at post-ECT assessment and study endpoint. Eighteen RCTs (n = 1769) with 20 active treatment arms were identified and meta-analyzed. Adjunctive ECT was superior to clozapine regarding symptomatic improvement at post-ECT assessment (Standardized Mean Difference (SMD) = -0.88, 95% Confidence Interval (CI): −1.33 to −0.44; I^2 = 86%, P = 0.0001) and endpoint assessment (SMD: −1.44, 95%CI: −2.05 to −0.84; I^2 = 95%, P < 0.00001), separating as early as week 1–2 (SMD = −0.54, 95%CI: −0.88 to −0.20; I^2 = 77%, P = 0.002). Adjunctive ECT was also superior regarding study-defined response at post-ECT assessment (53.6% vs. 25.4%, Risk Ratio (RR) = 1.94, 95%CI: 1.59–2.36; I^2 = 0%, P < 0.00001, number-needed-to-treat (NNT) = 3, 95%CI: 3–5) and endpoint assessment (67.7% vs. 41.4%, RR = 1.66, 95%CI: 1.38–1.99; I^2 = 47%, P < 0.00001, NNT = 4, 95%CI: 3–8), and remission at post-ECT assessment (13.3% vs. 3.7%, RR = 3.28, 95%CI: 1.80–5.99; I^2 = 0%, P = 0.0001, NNT = 13, 95%CI: 6–100) and endpoint assessment (23.6% vs. 13.3%, RR = 1.80, 95%CI: 1.39 to 2.35; I^2 = 5%, P < 0.0001, NNT = 14, 95%CI: 6–50). Patient-reported memory impairment (24.2% vs. 0%; RR = 16.10 (95%CI: 4.53–57.26); I^2 = 0%, P < 0.0001, number-needed-to-harm (NNH) = 4, 95%CI: 2–14) and headache (14.5% vs 1.6%; RR = 4.03 (95%CI: 1.54–10.56); I^2 = 0%, P = 0.005, NNH = 8, 95%CI: 4–50) occurred more frequently with adjunctive ECT. No significant group differences were found regarding discontinuation and other adverse effects. Despite increased frequency of self-reported memory impairment and headache, ECT augmentation of clozapine is a highly effective and relatively safe treatment for CRS.
Registration number: CRD42018089959

1. Introduction

Schizophrenia is a severe and chronic psychiatric illness that is characterized by positive, negative and cognitive symptoms. Depending on the definition, setting and population, approximately 30% and up to 70% of patients with schizophrenia are resistant to first-line antipsychotic treatments (Howes et al., 2017).

Clozapine, an atypical antipsychotic, is the treatment of choice for

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https://doi.org/10.1016/j.jpsychires.2018.08.002
Received 19 March 2018; Received in revised form 5 July 2018; Accepted 1 August 2018

treatment-resistant schizophrenia (TRS) (Attard and Taylor, 2012; Kane et al., 1988; Lewis et al., 2006; McEvoy et al., 2006; Samara et al., 2016; Siskind et al., 2017). Clozapine is superior to other antipsychotics in terms of symptomatic improvement, less hospitalization and mortality risk, as well as improved social functioning (Meltzer, 1992; Meltzer and Okayli, 1995; Taipale et al., 2017; Vermeulen et al., 2018). A network meta-analysis of randomized clinical trials (RCTs) in non-treatment-resistant schizophrenia (Leucht et al., 2013) supported the greater efficacy of clozapine over other antipsychotics in schizophrenia. However, meta-analytic evidence from RCTs in treatment-resistant samples was more mixed (Siskind et al., 2016; Samara et al., 2016), yet, methodological issues, inclusion of non-refractory patients and low clozapine doses may account for these inconsistent findings (Kane and Correll, 2016). Nevertheless, a review of effectiveness trials (Attard and Taylor, 2012) and other national database studies (Taipale et al., 2017; Tiihonen et al., 2009, 2011, 2017) confirmed the superior effectiveness of clozapine in schizophrenia. However, despite its superior efficacy, only a small number of patients receive clozapine, and only 30%–60% of patients with TRS benefit from clozapine monotherapy (Havaki-Kontaxaki et al., 2006; Kane et al., 1988; Meltzer et al., 1989), converging on 40% in a recent meta-analysis (Siskind et al., 2017). Unfortunately, despite superior efficacy and effectiveness of clozapine in TRS (Siskind et al., 2017), it remains underutilized (Bachmann et al., 2017). Clozapine is associated with certain severe adverse events, such as neutropenia, agranulocytosis, and increased mortality rate, which limits its wide use, although most of these adverse effects are monitorable and addressable (Nielsen et al., 2013). Moreover, clozapine requires routine hematologic monitoring in clinical practice (Nielsen et al., 2016), which can further detract from its use (Remington et al., 2016). Although a number of pharmacologic augmentation strategies including antipsychotics (such as amisulpride), antidepressants (such as mirtazapine), mood stabilizers (such as lamotrigine) and other agents (such as fatty acid supplement and glutamatergic agents) have been tried in patients with clozapine-resistant schizophrenia (CRS) (Porcelli et al., 2012; Sommer et al., 2012; Taylor et al., 2012; Veerman et al., 2014), none has sufficient meta-analytic evidence to be uniformly endorsed (Correll et al., 2017; Veerman et al., 2017).

Electroconvulsive therapy (ECT) has been used for more than 70 years in the treatment of a variety of psychiatric disorders, including mood disorders and schizophrenia (Weiner, 2008). However, one earlier meta-analysis with very limited data compared the effect of ECT monotherapy (studies = 10, n = 443) and augmentation treatment (acute treatment studies = 1, n = 40) with antipsychotic monotherapy in schizophrenia, finding inconclusive results (Tharyan and Adams, 2005). A more recent meta-analysis focused on non-clozapine TRS and found superior efficacy of ECT augmentation vs continued antipsychotic treatment (Zheng et al., 2017). Nevertheless, ECT combination with clozapine may also be an effective treatment for CRS (Kho et al., 2004). This possibility is suggested by a number of case reports (Bhatia et al., 1998; Biedermann et al., 2011; Gerretsen et al., 2011; Husni et al., 1999; Safferman and Munne, 1992), cases series (Benatov et al., 1996; Kales et al., 1999; Kurian et al., 2005), and several recent meta-analytic reviews (Ahmed et al., 2017; Lally et al., 2016) that mixed ECT augmentation of non-clozapine and clozapine-resistant schizophrenia together (Wang et al., 2015).

ECT has been widely used for TRS in China, and it is one of the most commonly used therapeutic strategies for the treatment of CRS (Zhang et al., 2010). A number of RCTs of ECT augmentation of clozapine versus clozapine monotherapy for TRS have been conducted in China (Cai et al., 2008; Du et al., 2011; Liu, 2013; Lou et al., 2013; Miyamoto et al., 2015; Wan et al., 2009; Wang et al., 2011; Xiang et al., 2017; Xiong and Liu, 2015; Yang et al., 2005; Yu et al., 2015; Zeng and Liao, 2010; Zhang et al., 2010, 2011; Zhao et al., 2012).

While a number of Chinese RCTs have found the ECT-clozapine combination to be superior to clozapine monotherapy for TRS (Chen, 2012; Du et al., 2011; Liu, 2013; Lou et al., 2013), non-Chinese studies have been limited largely to either case reports (Benatov et al., 1996; Bhatia et al., 1998; Biedermann et al., 2011; Gerretsen et al., 2011; Husni et al., 1999; Kales et al., 1999; Kurian et al., 2005; Masiar and Johns, 1991; Safferman and Munne, 1992), one open-label trial (Kho et al., 2004), while only two non-Chinese RCTs exist (Masoudzadeh and Khalilian, 2007; Petrides et al., 2015), both with small sample sizes. So far, there have been few reviews evaluating the efficacy and safety of ECT combined with clozapine in patients with TRS (Havaki-Kontaxaki et al., 2006; Kales et al., 1999; Lally et al., 2016; Porcelli et al., 2012) and data on the efficacy and safety of ECT combination with clozapine for TRS are still limited. Recent RCTs of ECT-clozapine combination for TRS published in Chinese are generally not accessible to the international readership and have not been included in prior meta-analytic reviews (Ahmed et al., 2017; Lally et al., 2016), except few ones (Kittsteiner Manubens et al., 2016).

We conducted a meta-analysis to comprehensively assess the efficacy and safety of electroconvulsive therapy augmentation of clozapine for clozapine-resistant schizophrenia. We hypothesized that based on data in treatment-resistant schizophrenia not resistant to clozapine (Zheng et al., 2017), augmentation of clozapine with ECT would be superior to continued clozapine treatment, being also sufficiently tolerable and safe.

2. Methods

2.1. Types of studies

Only published RCTs which reported the efficacy and/or safety of ECT added to clozapine for TRS were eligible for inclusion in this meta-analysis. Case series, retrospective studies, open-label prospective trials, RCT (Masoudzadeh and Khalilian, 2007) without meta-analyzable data, meta-analyses and systematic reviews were excluded.

2.2. Outcome measures

We recorded clinical outcomes based on intent to treat (ITT) analysis (preferred) or last-observation-carried-forward (LOCF) data. The co-primary outcome measures were total psychopathology at post-ECT and endpoint assessments measured using a standardized and detailed rating scale, such as the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), or Brief Psychiatric Rating Scale (BPRS) (Overall and Beller, 1984). Key secondary outcomes included 1) early symptomatic improvement (at 1–2 weeks), 2) study-defined response at post-ECT and endpoint assessments, 3) study-defined remission (using the definitions by authors of included studies) at post-ECT and endpoint assessments, 4) specific response (≥50% reduction in total PANSS or BPRS) and remission (≥75% reduction in total PANSS or BPRS) at post-ECT treatment and endpoint assessments, 5) positive, negative, or general symptom scores assessed by PANSS or BPRS or the total scores of the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and/or the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) at post-ECT treatment and endpoint assessment, 6) patient-reported adverse events, 7) neurocognitive functioning, and 8) treatment discontinuation. In some studies, patients were not followed up after the last ECT treatment. In order not to mix post-ECT and endpoint assessments, treatment efficacy at endpoint assessments was calculated only based on studies with ≥1 additional post-ECT follow-up visit.

2.3. Search

PubMed, PsycINFO, Cochrane Library databases and Chinese databases (Chinese Biomedical database (CBM), China Journal Net and WanFang database) were searched. The search included all studies published in English and Chinese language until December 24, 2017. The keywords used for the searches included: (Clozapine OR Clozaril)

AND ((Electric Convulsive Therap* OR Therap*, Electric Convulsive) OR Electroshock Therap* OR Convulsive Therap*, Electric OR Electroconvulsive Therap* OR Therap*, Electroconvulsive OR Electric Shock Therap* OR Shock Therap*, Electric OR Therap*, Electric Shock OR Therap*, Electroshock) AND (Schizophrenic Disorder OR Disorder, Schizophrenic OR Schizophrenic Disorders OR Schizophrenia OR Dementia Praecox). The search was supplemented by using the "related article" function. We also manually searched bibliographies of pertinent RCTs, meta-analyses and systematic reviews for additional studies.

2.4. Data extraction

Three authors (WZ, S-BW and X-BL) independently conducted the literature search and extracted the data for all outcome measures listed above. Thereafter, one author (Y-TX) checked the data again. Any disagreement was resolved through discussion and consensus. Data were extracted into simple, standardized forms. Data presented only in graphs and figures were extracted whenever possible, but included only if the three authors independently came to the same conclusion. Authors were contacted to obtain missing information or clarification. If case of multicenter studies, whenever possible, data were extracted separately for each center (Higgins and Green, 2008).

2.5. Assessment of the methodological quality of RCTs

The methodological quality of RCTs was assessed using both the Cochrane risk of bias-version 1.0 and the Jadad scale that ranges from 0 to 5 (Jadad et al., 1996). Furthermore, the grading of recommendations assessment, development, and evaluation (GRADE) system was employed to rate the quality of evidence and the strength of recommendations of the meta-analytic outcomes as recommended by the Cochrane Collaboration (Atkins et al., 2004; Balshem et al., 2011).

2.6. Statistical methods

The meta-analysis was performed according to the recommendations of the Cochrane Collaboration, using the Review Manager Version 5.3 software and Comprehensive Meta-analysis Version 2 software. For meta-analytic pooling of continuous outcomes, the Inverse-Variance method was used and standardized mean differences (SMDs) with their 95% confidence intervals (CIs) are reported. Summary statistics of dichotomous outcomes are presented as risk ratio (RR) ± 95%CIs using the Mantel-Haenszel test. When RRs were significant, we calculated the number-needed-to-treat (NNT) or number-needed-to-harm (NNH) by dividing 1 by the risk difference. The I^2 method was used to assess statistical heterogeneity. All statistical differences were considered significant when $P < 0.05$.

When combining studies for the meta-analysis, a random effects model was used in all cases. In case of $I^2 \geq 50\%$ for the effect of ECT augmentation of clozapine on symptomatic improvement at post-ECT assessment or endpoint assessment, we conducted a sensitivity analysis, repeating the analyses for each of the respective efficacy endpoints and/or time points after removing 2 and 4 studies (depending on the outcome), which had an outlying effect size of SMD- > 1.5 (Wan et al., 2009; Xia, 2016; Xiong and Liu, 2015; Yang et al., 2005; Yu et al., 2015; Zhang et al., 2010), respectively. Furthermore, we conducted 9 subgroup analyses, in order to identify potential moderators or mediators of the effect on symptomatic improvement at post-ECT assessment and endpoint assessment. These subgroup and sensitivity analysis included: (1) Chinese studies vs. non-Chinese studies; (2) rater-masked vs. non-blinded studies; (3) studies describing randomization details vs. those not describing randomization details; (4) patients with failure to ≥2 antipsychotics (APs) vs. failure to ≥3 APs; (5) study duration of 8 weeks vs. 12 weeks; (6) mean number of ECT treatments < 9 ECTs vs. ≥9 (since the number of ECT treatments was reported inconsistently (range, minimum number, fixed number, etc), we used the median split of the number of recommended ECT treatments per the ECT guidelines for adults in China, i.e., 6 to 12 sessions) (Chen, 2009); (7) mixed models or LOCF vs. observed cases analysis, (8) male predominance (> 60% male) vs. male proportion ≤60%; and (9)bilateral vs. unilateral electrode placement.

Moreover, two studies (Wan et al., 2009; Yu et al., 2015) included three study arms. We compared each of the 2 active co-treatment arms with the control group separately by including the clozapine monotherapy condition twice in the analysis, but assigning half of the total patients of the clozapine monotherapy group randomized to each clozapine arm in order to not inflate the number of monotherapy patients.

Furthermore, using Comprehensive Meta-Analysis Version 2 (Biostat, http://www.meta-analysis.com), we conducted meta-regression analyses to test the potential effect of 1) sample size; 2) trial duration; 3) mean patient age; 4) percent of males; 5) illness duration; 6) clozapine dose of ECT-clozapine combination; 7) number of ECT treatment session; 8) study quality score (Jadad score); and 9) baseline PANSS total score or converted PANSS total score from BPRS total score using an established conversion scheme (Lally et al., 2016). Subgroup and meta-regression analyses were not performed for study-defined response and remission at post-ECT assessment and endpoint assessment, as the heterogeneity was small (I^2 = 0%–34%).

Finally, publication bias was assessed for the primary outcome using funnel plots, Egger's test (Egger et al., 1997). Furthermore, we used Rosenthal's fail-safe method (Ferentinos and Kontaxakis, 2003) to estimates the number of studies needed to change the findings to meet or not meet the alpha of 0.05.

3. Results

3.1. Search results

The search yielded 460 potentially relevant articles, of which 254 articles were in English and 206 articles were in Chinese. Of the 410 studies, 18 RCTs (Cai et al., 2008; Chen, 2012; Du et al., 2011; Liu, 2013; Liu et al., 2015; Lou et al., 2013; Petrides et al., 2015; Wan et al., 2009; Wang et al., 2011; Xia, 2016; Xiong and Liu, 2015; Yang et al., 2005; Yu et al., 2015; Zeng and Liao, 2010; Zhang, 2017; Zhang et al., 2010, 2011; Zhao et al., 2012) with 20 active treatment arms met study entry criteria and were included for analyses (for details, see Fig. S1).

3.2. Study characteristics

Eighteen RCTs with 20 active treatment arms (n = 1769) had a mean sample size of 88.5 ± 41.7 (range = 39–246, median = 79) patients, and lasted 9.2 ± 2.6 (range = 4–12, median = 8) weeks (Table S1). Seventeen RCTs were conducted in China, and one in the USA. All participants had a diagnosis of TRS and resistance definitions included failure of treatment with ≥2 APs (4 RCTs), ≥3 APs (11 RCTs), or non-specific definition (3 RCTs). In studies with available information, participants were 38.2 ± 5.2 (range = 26.5–48.8, median = 37.8) years old, and 55.0 ± 8.6% were male. Clozapine dosages ranged from 50 to 800 mg/day (median = 355 mg/day) in the clozapine monotherapy group. Moreover, clozapine dosages ranged from 50 to 700 mg/day (median = 337.5 mg/day) in the ECT-clozapine group. ECT treatment sessions ranged from 6 to 24 (median = 10.8).

3.3. Quality assessment

While the literature search yielded 18 RCTs with meta-analyzable data on ECT augmentation of clozapine for TRS (Table S1), only 3 RCTs (16.7%) described an adequate method of random sequence generation, whereas 13 RCTs (72.2%) only mentioned "random" assignment without any further, specific description. None of the studies detailed whether allocation concealment was implemented or whether there was a high risk for not blinding patients (i.e. not using sham ECT). Only

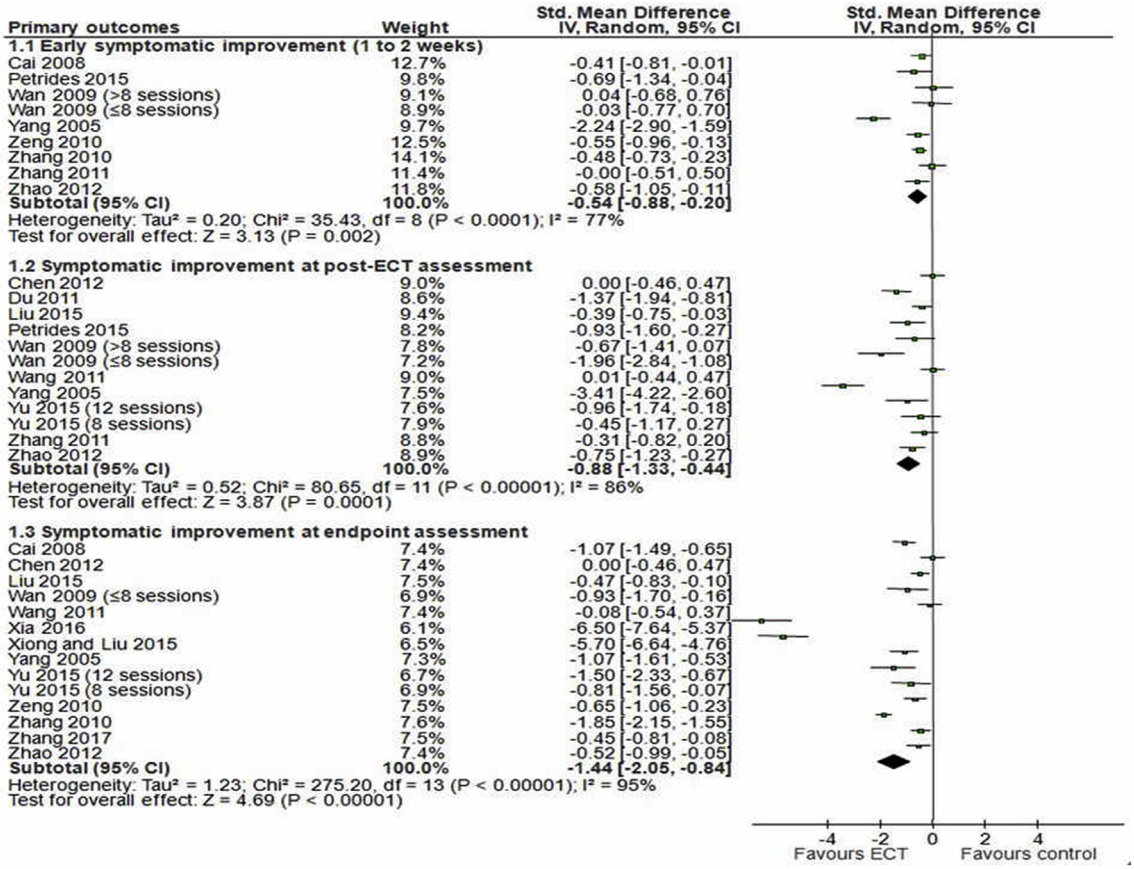

Fig. 1. Global Symptomatic Improvement at 1–2 Weeks, post-ECT Assessment and Endpoint Assessment.

one RCT used masked assessors, while blinding of the assessments was rated as high risk in the other RCTs. Only 4 studies (25.0%) with 5 active treatment arms reported data on loss to follow-up, and one study was rated as unclear for incomplete outcome data. None of the studies employed a protocol registration, which did not allow us to formally assess the potential for selective reporting (Fig. S2).

Quality assessment of the studies according to the GRADE approach showed some limitations and inconsistency of the study design, some strengths in terms of large treatment effect, and no obvious indirectness or imprecision in reporting of the results. Altogether, the quality of evidence presented for 30 outcomes ranged from "very low" (13.3%), "low" (26.7%), moderate (43.3%) to "high" (16.7%) (Table S2). Using the Jadad scale, study quality ranged from 1 to 3 (mean = 2.1 ± 0.6; median = 2 out of a maximum quality score of 5) (Table S1).

3.4. Treatment efficacy

Combined ECT-clozapine treatment (n = 384) was superior to clozapine monotherapy (n = 355) regarding early symptomatic improvement (1–2 weeks; 8 RCTs with 9 active treatment arms, SMD: 0.54, 95%CI: −0.88 to −0.20; I^2 = 77%, P = 0.002, Fig. 1).

At post-ECT assessment: Regarding overall symptomatic status after a treatment duration of 4–12 weeks (mean = 5.8 weeks), combined ECT-clozapine treatment (n = 386) was superior to clozapine monotherapy (n = 317) (10 RCTs with 12 active treatment arms, SMD: −0.88, 95%CI: −1.33 to −0.44; I^2 = 86%, P = 0.0001) (Fig. 1). Results for overall symptomatic status remained significant when two strong outlying study arms (Wan et al., 2009; Yang et al., 2005) were removed (10 active treatment arms, SMD: 0.54 (95%CI: 0.82,-0.26), P = 0.0001; I^2 = 62%). Superiority of combined ECT-clozapine treatment was confirmed in 14 of the 17 analyzed subgroups with meta-analyzable data (Table 1). Statistical significance changed to a statistical trend only for patients with failure to ≥2 APs (P = 0.09), studies with male preponderance (P = 0.08) and electrode placement using bilateral (P = 0.06).

In exploratory meta-regression analyses, there was a significantly inverse relationship between four pre-defined variables (sample size: P = 0.0035, illness duration: P < 0.00001, ECT treatment session: P = 0.018, trial duration: P < 0.00001) and the efficacy of combined ECT-clozapine treatment for symptomatic improvement at post-ECT assessment. Higher clozapine dose in the ECT-clozapine combination group (P = 0.00025) was significantly associated with greater symptomatic improvement, but mean patient age (P = 0.103), study quality score (Jadad score) (P = 0.285), baseline PANSS total score (P = 0.060) and percentage of males (P = 0.199) were not significantly associated with symptomatic improvement.

Upon visual inspection, the funnel plots were asymmetrical for symptomatic improvement at post-ECT assessment. Accordingly, Egger's test revealed presence of publication bias (P = 0.022). The fail-safe method indicated that 265 additional studies would be required to lead to a non-significant finding.

Similar results were found regarding study-defined response, i.e., reduction in PANSS or BPRS total score ≥50% (7 RCTs) or BPRS total score ≥40% (1 RCT) or not report definition (2 RCTs) (53.6% vs. 25.4%, RR = 1.94, 95%CI: 1.59–2.36; I^2 = 0%, P < 0.00001, NNT = 3, 95%CI: 3–5) (Fig. 2) and remission, i.e., ≥75% (6 RCTs), ≥70% (2 RCTs) or not report definition (1 RCT) reduction in PANSS or BPRS total score: 13.3% vs. 3.7%, RR = 3.28, 95%CI: 1.80–5.99; I^2 = 0%, P = 0.0001, NNT = 13, 95%CI: 6–100) (Fig. 2).

The results were consistent for specific and rigorous definitions of response (≥50% reduction in total PANSS) (RR = 2.14, 95%CI: 1.62–2.83; I^2 = 0%, P < 0.00001, NNT = 3, 95%CI: 3–5) (Table 2) and remission (≥75% reduction in total PANSS) (RR = 3.95, 95%CI: 1.88–8.30; I^2 = 0%, P = 0.0003, NNT = 8, 95%CI: 4-∞) (Table 2).

Table 1
Subgroup analysis and Sensitivity analysis of endpoint symptomatic improvement at post-ECT assessment and endpoint assessment.

Variables	Symptomatic improvement at post-ECT assessment				
	Subjects (active treatment arms)	SMDs (95%CI)	I^2 (%)	P-value within subgroup	P-value across subgroups
1. Chinese studies	664 (11)	−0.88 (−1.36, −0.40)	87	**0.0003**	0.91
Non-Chinese studies	39 (1)	−0.93 (−1.60, −0.27)	N/A	**0.006**	
2. Rater masked	39 (1)	−0.93 (−1.60, −0.27)	N/A	**0.006**	0.91
Open label	664 (11)	−0.88 (−1.36, −0.40)	87	**0.0003**	
3. Describing randomization details	78 (2)	−0.69 (−1.22, −0.15)	0	**0.01**	0.31
Not describing randomization details	625 (10)	−0.92 (−1.44, −0.41)	89	**0.0005**	
4.Failure to ≥ 2 APs	170 (2)	−0.75 (−1.62, 0.12)	86	0.09	0.31
Failure to ≥ 3 APs	413 (8)	−1.02 (−1.70, −0.35)	89	**0.003**	
5.8 weeks duration	309 (5)	−1.29 (−2.02, −0.56)	87	**0.0005**	0.68
12 weeks duration	394 (6)	−0.45 (−0.86, −0.04)	73	**0.03**	
6. Number of ECTs (< 9 ECTs)[a]	109 (3)	−1.00 (−1.86, −0.13)	73	**0.02**	0.32
Number of ECTs (≥9 ECTs)[a]	594 (9)	−0.85 (−1.38, −0.32)	89	**0.002**	
7. Last observation carried forward	565 (9)	−1.00 (−1.57, −0.42)	90	**0.0007**	0.09
Observed cases	138 (3)	−0.49 (−0.86, −0.12)	0	**0.009**	
8. Male predominance (> 60%)	159 (3)	−1.53 (−3.23, 0.17)	95	0.08	0.27
Males≤ 60%	406 (6)	−0.53 (−0.97, −0.10)	76	**0.02**	
9. Bilateral ECT	99 (2)	−0.58 (−1.19, 0.02)	53	0.06	NA
Unilateral ECT	No data	No data	No data	No data	
Variables	Symptomatic improvement at study endpoint				
	Subjects (active treatment arms)	SMDs (95%CI)	I^2 (%)	P-value	P-value
1. Chinese studies	1235 (14)	−1.44 (−2.05, −0.84)	95	< **0.00001**	N/A
Non-Chinese studies	No data	No data	No data	No data	
2. Rater masked	No data	No data	No data	No data	N/A
Open label	1235 (14)	−1.44 (−2.05, −0.84)	95	< **0.00001**	
3. Describing randomization details	286 (4)	−2.09 (−4.09, −0.08)	97	**0.04**	0.41
Non-describing randomization details	949 (10)	−1.20 (−1.83, −0.57)	95	**0.0002**	
4.Failure to ≥ 2 APs	162 (2)	−2.83 (−8.42, 2.76)	99	0.32	0.50
Failure to ≥ 3 APs	875 (10)	−0.88 (−1.28, −0.48)	86	< **0.0001**	
5.8 weeks duration	469 (6)	−2.21 (−3.78, −0.64)	98	**0.006**	0.14
12 weeks duration	766 (8)	−0.98 (−1.41, −0.56)	85	< **0.00001**	
6. Number of ECTs (< 9 ECTs)[a]	74 (2)	−0.87 (−1.40, −0.33)	0	**0.001**	0.12
Number of ECTs (≥9 ECTs)[a]	1161 (12)	−1.54 (−2.22, −0.87)	96	< **0.00001**	
7. Last observation carried forward	913 (11)	−1.47 (−2.19, −0.75)	96	< **0.0001**	0.97
Observed cases	322 (3)	−1.45 (−2.09, −0.81)	70	< **0.00001**	
8. Male predominance (> 60%)	154 (2)	−0.82 (−1.23, −0.41)	31	< **0.0001**	0.08
Males≤ 60%	1081 (12)	−1.56 (−2.27, −0.85)	96	< **0.0001**	
9. Bilateral ECT	363 (2)	−1.15 (−2.52, 0.22)	97	0.10	N/A
Unilateral ECT	No data	No data	No data	No data	

Bolded p-values: $P < 0.05$.
APs = antipsychotics; N/A = Not applicable; SMDs = standardized mean differences.
[a] Using the median split of the number of recommended ECT treatments per the ECT guidelines for adults in China, i.e., 6 to 12 sessions.

Meta-analysis of positive symptom scores found an advantage of combined ECT-clozapine treatment compared with clozapine monotherapy (SMD: −0.45, 95%CI: −0.68 to −0.22; I^2 = 8%, P = 0.0001, Table 2), but not for negative or general symptom scores (Table 2).

At endpoint assessment: Regarding overall symptomatic status after follow-up post-ECT of 1–10 weeks (mean = 5.3 weeks), combined ECT-clozapine treatment (n = 646) was superior to clozapine monotherapy (n = 589) (13 RCTs with 14 active treatment arms, SMD: −1.44, 95%CI: −2.05 to −0.84; I^2 = 95%, P < 0.00001) (Fig. 1). Results for overall symptomatic status remained significant when four strong outlying study studies (Xia, 2016; Xiong and Liu, 2015; Yu et al., 2015; Zhang et al., 2010) were removed (10 active treatment arms, SMD: 0.57 (95%CI: 0.80, −0.34), P < 0.00001; I^2 = 57%). Superiority of combined ECT-clozapine treatment was confirmed in 13 of the 15 analyzed subgroups (Table 1). Significance disappeared only for patients with failure to ≥2 APs (P = 0.32) and studies with use of bilateral electrode placement (P = 0.10).

In exploratory meta-regression analyses, there was a significantly inverse relationship between four pre-defined variables (illness duration: P < 0.00001, baseline PANSS total score: P < 0.00001, percentage of males: P = 0.004, trial duration: P < 0.00001) and the efficacy of combined ECT-clozapine treatment for symptomatic improvement at endpoint assessment. Higher clozapine dose in the ECT-clozapine combination group (P = 0.0006) and larger sample size (P < 0.00001) were significantly associated with greater symptomatic improvement, but the number of ECT treatment session (P = 0.747), study quality score (Jadad score) (P = 0.06), and mean patient age (P = 0.197) were not.

On visual inspection, the funnel plots were symmetrical for symptomatic improvement at endpoint assessment. Accordingly, Egger's test did not find potential publication bias (P = 0.095). The fail-safe method indicated that 1037 additional studies would be required to lead to a non-significant finding.

Similar results were found regarding study-defined response, i.e., reduction in PANSS or BPRS total score ≥50% (6 RCTs with 7 active treatment arms) or based on clinical observation (1 RCT), or without reported definition (1 RCT) (67.7% vs. 41.4%, RR = 1.66, 95%CI: 1.38–1.99; I^2 = 47%, P < 0.00001, NNT = 4, 95%CI: 3–8) (Fig. 3). The same was true for remission, i.e., ≥75% reduction in PANSS or BPRS total score (6 RCTs with 7 active treatment arms) or based on clinical observation (1 RCT), or without reported definition (1 RCT): 23.6% vs. 13.3%, RR = 1.80, 95%CI: 1.39 to 2.35; I^2 = 5%, P < 0.0001, NNT = 14, 95%CI: 6–50, Fig. 3).

The results were consistent for specific and robust response (≥50% reduction in total PANSS) (RR = 1.61, 95%CI: 1.20–2.16; I^2 = 0%, P = 0.002, NNT = 7, 95%CI: 3-∞) (Table 2), but not for remission

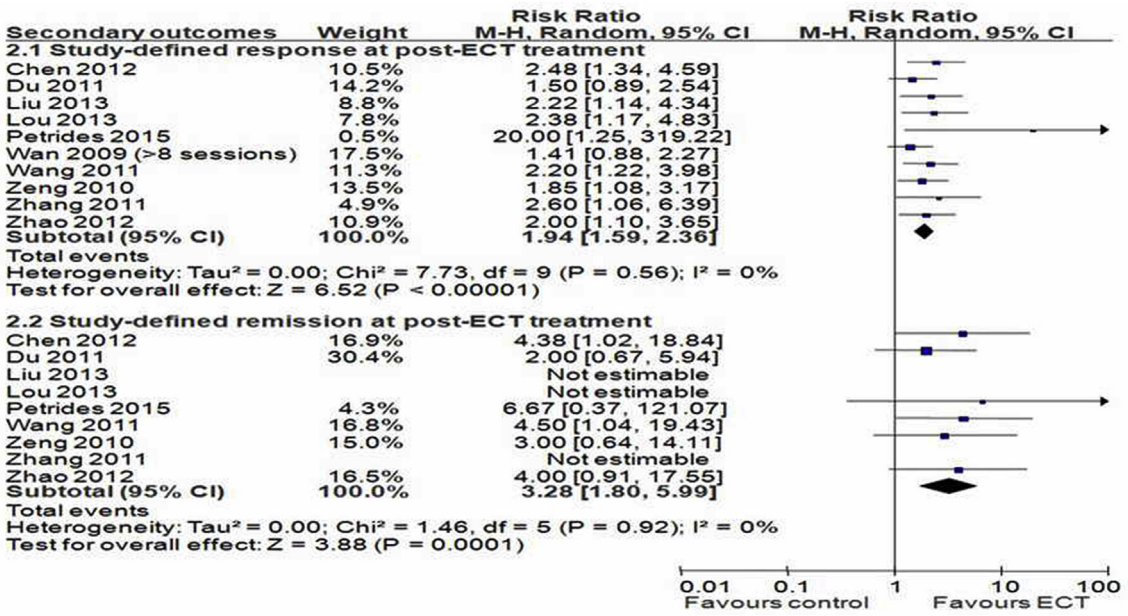

Fig. 2. Study-defined Response and Remission at post-ECT Assessment.

(≥75% reduction in total PANSS) (RR = 1.29, 95%CI: 0.84–1.98; I^2 = 0%, P = 0.25) (Table 2).

Meta-analysis of positive symptom scores found an advantage of combined ECT-clozapine treatment compared with clozapine monotherapy (SMD: −0.46, 95%CI: −0.78 to −0.15; I^2 = 53%, P = 0.004, Table 2), but not for negative and general symptom scores (Table 2).

3.5. Adverse events

Memory impairment (RR = 16.10, 95%CI: 4.53–57.26; I^2 = 0%, P < 0.0001, NNH = 4, 95%CI: 2–14) and headache (RR = 4.03, 95%CI: 1.54–10.56; I^2 = 0%, P = 0.005, NNH = 8, 95%CI: 4–50) were significantly more often spontaneously reported in the ECT-clozapine group than in the clozapine monotherapy group. Conversely, patient-reported weight gain (RR = 0.61, 95%CI: 0.42–0.89; I^2 = 0%, P = 0.01, NNT = 14, 95%CI: 8–100) and constipation (RR = 0.77, 95%CI: 0.61–0.99; I^2 = 0%, P = 0.04, NNT = 14, 95%CI: 7–100) was significantly less frequently reported with ECT-clozapine group compared to the clozapine monotherapy group (Table 2).

Meta-analysis of salivation, leukocytopenia, drowsiness, elevated liver enzymes, nausea/vomiting, and tachycardia revealed no significant group differences (RR = 0.68–1.65, 95%CI: 0.22–4.27; I^2 = 0%–41%, P = 0.05–0.74) (Table 2).

Table 2
Secondary outcomes: ECT combined with clozapine for treatment-resistant schizophrenia.

Variables	Subjects (active treatment arms)	SMDs or RRs (95%CI)	I^2 (%)	P-value
Clinical efficacy				
Response (≥50% reduction in total PANSS) at post-ECT assessment	371 (5)	2.14 (1.62, 2.83)	0	**< 0.00001**
Remission (≥75% reduction in total PANSS) at post-ECT assessment	371 (5)	3.95 (1.88, 8.30)	0	**0.0003**
Positive symptom scores at post-ECT treatment	355 (6)	−0.45 (−0.68, −0.22)	8	**0.0001**
Negatvie symptom scores at post-ECT treatment	355 (6)	−0.24 (−0.49, 0.01)	25	0.06
General symptom scores at post-ECT treatment	355 (6)	−0.12 (−0.77, 0.53)	88	0.72
Response (≥50% reduction in total PANSS) at endpoint assessment	248 (4)	1.61 (1.20,2.16)	0	**0.002**
Remission (≥75% reduction in total PANSS) at endpoint assessment	326 (5)	1.29 (0.84, 1.98)	0	0.25
Positive symptom scores at endpoint assessment	389 (6)	−0.46 (−0.78, −0.15)	53	**0.004**
Negatvie symptom scores at endpoint assessment	389 (6)	−0.28 (−0.59, 0.04)	53	0.08
General symptom scores at endpoint assessment	389 (6)	−0.33 (−0.91, 0.24)	86	0.26
Patient-reported Adverse Effects				
Memory impairment	372 (5)	16.10 (4.53, 57.26)	0	**< 0.0001**
Headache	372 (5)	4.03 (1.54, 10.56)	0	**0.005**
Weight gain	540 (7)	0.61 (0.42, 0.89)	0	**0.01**
Constipation	540 (7)	0.77 (0.61, 0.99)	12	**0.04**
Salivation	540 (7)	0.76 (0.58, 1.00)	0	0.05
Leukocytopenia	277 (4)	0.78 (0.22, 2.75)	0	0.70
Drowsiness	462 (6)	0.80 (0.60, 1.07)	41	0.14
Elevated liver enzymes	431 (6)	0.68 (0.36, 1.28)	0	0.23
Nausea/vomiting	226 (3)	1.65 (0.64, 4.27)	0	0.30
Tachycardia	371 (5)	0.95 (0.69, 1.30)	0	0.74
Neurocognitive functioning				
Memory Quotient (MQ) at post-ECT Assessment	78 (2)	0.02 (−0.49, 0.54)	0	0.93
Memory Quotient (MQ) at endpoint assessment	78 (2)	0.13 (−0.39, 0.65)	0	0.62
Treatment discontinuation				
All-cause discontinuation at endpoint assessment	457 (5)	0.95 (0.44, 2.05)	0	0.90

Abbreviations: CI = confidence interval, ECT = electroconvulsive therapy, PANSS = Positive and Negative Syndrome Scale, RRs = risk radios, SMDs = Standard Mean Differences.

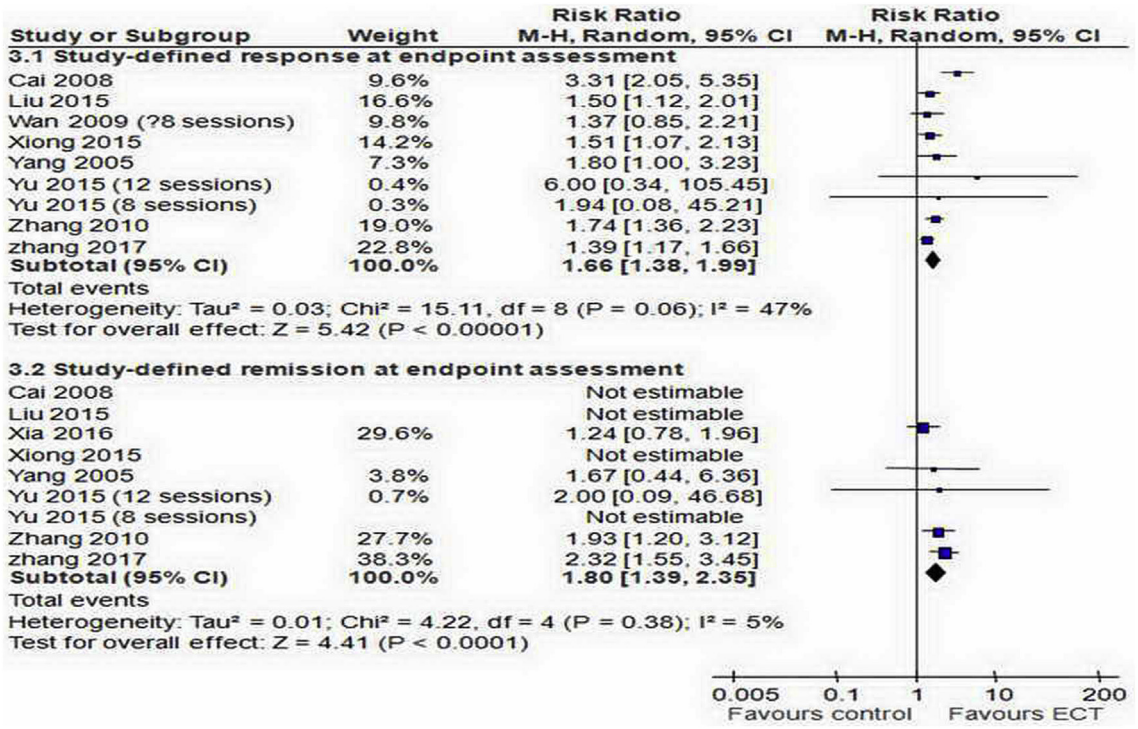

Fig. 3. Study-defined response and remission at endpoint assessment.

3.6. Neurocognitive functioning: Wechsler Memory Scale

Of the four RCTs (Wan et al., 2009; Wang et al., 2011; Yu et al., 2015; Zhang et al., 2010) with four treatment arms used the Wechsler Memory Scale (WMS), one study (Wang et al., 2011) did not provide data for the control group, and another study (Wan et al., 2009) with two active treatment arms had total scores that were entirely inconsistent with the literature (being about one third of usual scores), which found no significant group differences regarding WMS total score. One study (Zhang et al., 2010) did not provide data at ECT treatment endpoint and found a significant reduction of memory quotient (MQ) at one day after ECT treatment, but the statistical significance disappeared at one week after post-ECT assessment. Meta-analysis of MQ in one RCT (Yu et al., 2015) with two active treatment arms revealed no significant differences between the two active treatment groups at post-ECT assessment (N = 78, SMD = 0.02, 95%CI: −0.49 to 0.54; I^2 = 0%, P = 0.93) and endpoint assessment (N = 78, SMD = 0.13, 95%CI: −0.39 to 0.65; I^2 = 0%, P = 0.62) (Table 2).

3.7. Discontinuation rates

Meta-analysis of all-cause discontinuation at endpoint assessment revealed no significant group differences (4 RCTs with 5 active arms, N = 457, RR = 0.95, 95%CI: 0.44–2.05; I^2 = 0%, P = 0.90) (Table 2).

4. Discussion

This is the largest meta-analysis of the efficacy and safety of ECT augmentation of clozapine combination treatment in CRS. This meta-analysis identified 18 meta-analyzable RCTs, comprising 1769 patients. The main finding is that ECT added to clozapine had superior efficacy to clozapine monotherapy regarding the primary and all key secondary efficacy outcomes at post-ECT assessment and endpoint assessment, and that ECT augmentation of clozapine was safe and reasonably well tolerated. The reduction in total psychopathology was significantly superior to clozapine monotherapy as early as after 1–2 weeks with a moderate effect size of −0.54, which increased to a large effect size of −0.88 at post-ECT assessment after a mean duration of 5.8 weeks and of −1.44 at endpoint assessment after a mean follow-up with duration of 5.3 weeks. Despite heterogeneity of the co-primary outcome results, findings were consistent in sensitivity and subgroup analyses in 82.4% (14/17) and 86.7% (13/15) of the analyzed subgroups at post-ECT assessment and endpoint assessment, respectively.

Notably, after removing two (Wan et al., 2009; Yang et al., 2005) and four outlying studies (Xia, 2016; Xiong and Liu, 2015; Yu et al., 2015; Zhang et al., 2010) that had an effect size of SMD > −1.5 for overall symptomatic status at post-ECT assessment and endpoint assessment, respectively, the relevant effect size were still −0.54 or −0.57, and the heterogeneity decreased to 62% or 57%. This finding indicates that the heterogeneity of the significant pooled overall symptomatic status results at post-ECT assessment and endpoint assessment were not driven by outlying findings and that the heterogeneity was within the superior efficacy spectrum but not around the null hypothesis, further strengthening the results. In addition, meta-regression for overall symptomatic status at post-ECT assessment revealed that smaller sample size, shorter illness duration, fewer ECT treatment sessions, shorter trial duration, and higher clozapine dose in the ECT augmentation group were significantly associated with the efficacy of the ECT augmentation of clozapine. Although Egger's test showed an obvious publication bias for overall symptomatic status at post-ECT assessment, the fail-safe method indicated that 265 additional studies would have been required to lead to a non-significant finding.

Additionally, results at post-ECT assessment and endpoint assessment, respectively, were confirmed in key secondary outcome analyses of study-defined response and remission, as well as predefined, robust response (≥50% reduction in total PANSS) and remission (≥75% reduction in total PANSS), without significant heterogeneity.

In fact, the majority of CRS patients responded (at post-ECT assessment (53.6%, NNT = 3) and endpoint assessment (67.7%, NNT = 4)). However, only a relatively small proportion remitted at either the post-ECT assessment (13.3%, NNT = 13) and endpoint assessment (23.6%, NNT = 14), but with resultant NNTs that are still quite favorable for the most severe subgroup of patients with schizophrenia.

In addition to its efficacy, ECT augmentation of clozapine was generally safe and well-tolerated. Apart from 45 patients reporting memory impairment (24.2% vs. 0% on clozapine monotherapy) and 27 subjects who reported headache (14.5% vs 1.6% on clozapine monotherapy), which each were significantly more common in the ECT-clozapine group, there were no significant differences in other adverse events and treatment discontinuation between the ECT-clozapine and clozapine monotherapy groups. Only in one RCT (Petrides et al., 2015) one patient in the ECT-clozapine combination group experienced recurrence of preexisting involuntary "jerky" movements. Although there was a significant difference in memory functioning assessed with the Wechsler Memory Scale with adjunctive ECT after one day (Zhang et al., 2010), the difference was marginal and non-significant from one week onwards, which suggests that the memory impairment was mostly mild and tolerable and, importantly, transient (Lally et al., 2016). Similarly, one RCT (Yu et al., 2015) with 2 study arms found the two treatment groups without significant difference regarding MQ at post-ECT assessment and endpoint assessment. Thus, although memory impairment (NNH = 4) and headache (NNH = 8) were significantly more frequent with adjunctive ECT than clozapine monotherapy, these adverse effects do not seem to be not chronic and persistent, but rather transient and mild (Lou et al., 2013; Wang et al., 2011; Zhang et al., 2010).

The results of this meta-analysis support the findings of several previous systematic reviews (Ahmed et al., 2017; Havaki-Kontaxaki et al., 2006; Kupchik et al., 2000; Lally et al., 2016) that did not included Chinese studies. Moreover, results from this meta-analysis are broadly consistent with another recent meta-analysis (Zheng et al., 2017) of ECT added to non-clozapine antipsychotics for TRS, showing similar or even higher effect sizes for the most severe CRS cases compared to non-clozapine treated TRS cases. In that meta-analysis of 11 studies (n = 818) with a comparable mean trial duration (10.2 ± 5.5 vs CRS = 9.2 ± 2.6 weeks), adjunctive ECT was also superior to non-clozapine antipsychotic monotherapy regarding symptomatic improvement at last-observation endpoint with an SMD of −0.67 (CRS = −1.44), and also separating the two groups as early as week 1–2 with an SMD of −0.58 (CRS = −0.54). Furthermore, ECT was also superior at endpoint assessment regarding study-defined response (RR = 1.48, NNT of 6; CRS: RR = 1.74, NNT = 4) as well as remission (RR = 2.18; CRS: RR = 1.80), yet CRS patients were less likely to achieve remission than non-clozapine TRS patients (NNT = 14 vs. NNT = 8). However, different from the results in CRS, where only positive symptoms superiority was observed for the ECT augmentation of clozapine, in non-clozapine treated TRS patients, ECT augmentation was associated with significant improvements in general symptom subscores at endpoint too, yet, in neither patient group was ECT associated with significant improvements in negative symptoms. Finally, as in CRS patients, the ECT-augmentation of non-clozapine antipsychotics in TRS was also associated with significantly more headache (NNH = 6) and memory impairment (NNH of 3) (Zheng et al., 2017).

Several limitations of this study need to be acknowledged. First, there was significant heterogeneity of the meta-analytic results regarding endpoint overall symptomatic status, suggesting the effect of relevant moderator and mediator variables. Since a meta-analysis combines results from trials that differ in their methodology, study size, sampling, antipsychotic doses, ECT parameters and outcome variables, the random effects model was employed to provide a conservative estimate of all meta-analytic outcomes. Moreover, heterogeneity decrease from 86% to 62% after two strong outlying active treatment arms at post-ECT assessment and from 95% to 57% after four strong outlying active treatment arms at endpoint assessment with effect sizes > −1.5 were removed, confirming significant and clinically meaningful effects of ECT-clozapine cotreatment in the remaining studies.

Second, although this meta-analysis included 18 RCTs and 1769 patients, with > 1000 patients being considered necessary for robust meta-analytic results (Trikalinos et al., 2004), the sample sizes in some studies were small and the information for some outcomes was incomplete, reducing the number of analyzable studies and patients for primary and secondary outcomes. In addition, the Cochrane risk of bias - Version 2.0 (http://training.cochrane.org/resource/rob-20-webinar) was recently developed. It should be used in future meta-analysis after its psychometric properties have been adequately tested.

Third, although a strength of this study is the inclusion of Chinese databases that enabled us to identify RCTs not included in prior reviews, 17 of the included RCTs (94.4%) were conducted in China. Therefore, evidence for efficacy of ECT augmentation of clozapine treatment in non-Chinese settings and patients is incomplete and generalizability of the results requires further study.

Fourth, none of the RCTs used sham ECT and only one RCT (Petrides et al., 2015) reported blinding methods for raters in the quality assessment. According to the GRADE method, the quality of evidence was "moderate" and "low" regarding endpoint symptomatic improvement at both post-ECT assessment and endpoint assessment, and weeks 1–2 (mainly due to issues related to details on randomization schedule and blinding), respectively. The quality results for memory impairment and headache ranged from "moderate" to "high". Thus, higher quality studies are sorely needed to confirm and expand on the currently available evidence, even though sham ECT involving anesthesia is not without potential risk.

Fifth, the mean/medium duration of the studies was only 8–9 weeks. Thus, longer-term follow-up data are needed in order to assess if patients can maintain the gains that they achieved from ECT augmentation of clozapine, or whether maintenance ECT is required, whether remission rates could increase over time, and which patient and illness characteristics are predictive of one or the other outcome.

Finally, limited attention was given to the detailed assessment of cognitive side effects. Only 4 RCTs (Wan et al., 2009; Wang et al., 2011; Yu et al., 2015; Zhang et al., 2010) tested cognitive functions with the WMS, and one RCT (Petrides et al., 2015) employed the modified Mini-Mental State Examination (MMSE) that only captures marked cognitive dysfunction. Thus, the meta-analysis was restricted to patient-reported memory impairment. Future studies and meta-analyses of the ECT augmentation of clozapine in CRS and of non-clozapine antipsychotics for TRS will need to pay particular attention to cognitive side effects, both in terms of frequency, severity and durability/transience. However, a meta-analysis (Lally et al., 2016) suggests that the memory impairment and cognitive dysfunction following ECT is generally mild and short-lived.

5. Conclusions

TRS, especially CRS, is a complex, severe and disabling psychiatric disorder, which poses a significant therapeutic challenge (Howes et al., 2017; Kho et al., 2004). Results from this meta-analysis indicate that ECT added to clozapine for CRS is both effective, relatively safe and tolerable. Meta-analysis of improvement in psychiatric symptoms showed that adding ECT to clozapine was superior to monotherapy, yielding medium to large effect sizes at post-ECT assessment and endpoint assessment. Memory impairment and headache were the main adverse effects, but these symptoms were present in not more than 24.2% and 14.5% of patients receiving ECT augmentation and appeared to be mostly mild and transient. Additional, high quality studies are needed to determine the utility of ECT augmentation in patients with CRS.

Conflicts of interest

Dr. Correll has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Angelini, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, Medavante, Medscape, Merck, Neurocrine, Otsuka, Pfizer, ROVI, Servier, Sunovion, Takeda, and Teva. He has provided expert testimony

for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, ROVI and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a shareholder of LB Pharma. The other authors report no conflict of interest.

Funding sources

The study was supported by the University of Macau (MYRG2015-00230-FHS; MYRG2016-00005-FHS), National Key Research & Development Program of China (No. 2016YFC1307200), Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (No. ZYLX201607) and Beijing Municipal Administration of Hospitals' Ascent Plan (No. DFL20151801).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpsychires.2018.08.002.

References

Ahmed, S., Khan, A.M., Mekala, H.M., Venigalla, H., Ahmed, R., Etman, A., et al., 2017. Combined use of electroconvulsive therapy and antipsychotics (both clozapine and non-clozapine) in treatment resistant schizophrenia: a comparative meta-analysis. Heliyon 3, e00429.
Andreasen, N.C., 1983. Scale for the Assessment of Negative Symptoms (SANS). University of Iowa, Iowa City,IA.
Andreasen, N.C., 1984. Scale for the Assessment of Positive Symptoms (SAPS). University of Iowa, Iowa City,IA.
Atkins, D., Best, D., Briss, P.A., Eccles, M., Falck-Ytter, Y., Flottorp, S., et al., 2004. Grading quality of evidence and strength of recommendations. BMJ 328, 1490.
Attard, A., Taylor, D.M., 2012. Comparative effectiveness of atypical antipsychotics in schizophrenia: what have real-world trials taught us? CNS Drugs 26, 491–508.
Bachmann, C.J., Aagaard, L., Bernardo, M., Brandt, L., Cartabia, M., Clavenna, A., et al., 2017. International trends in clozapine use: a study in 17 countries. Acta Psychiatr. Scand. 136, 37–51.
Balshem, H., Helfand, M., Schunemann, H.J., Oxman, A.D., Kunz, R., Brozek, J., et al., 2011. GRADE guidelines: 3. Rating the quality of evidence. J. Clin. Epidemiol. 64, 401–406.
Benatov, R., Sirota, P., Megged, S., 1996. Neuroleptic-resistant schizophrenia treated with clozapine and ECT. Convuls Ther. 12, 117–121.
Bhatia, S.C., Bhatia, S.K., Gupta, S., 1998. Concurrent administration of clozapine and ECT: a successful therapeutic strategy for a patient with treatment-resistant schizophrenia. J. ECT 14, 280–283.
Biedermann, F., Pfaffenberger, N., Baumgartner, S., Kemmler, G., Fleischhacker, W.W., Hofer, A., 2011. Combined clozapine and electroconvulsive therapy in clozapine-resistant schizophrenia: clinical and cognitive outcomes. J. ECT 27, e61–e62.
Cai, X.Y., Liang, J.L., Su, Y., Zheng, Y.M., Luo, X.F., Yang, F.Y., et al., 2008. A comparison study of MECT combining clozapine in the treatment of treatment-resistant schizophrenia (In Chinese). Med. J. Chin. People's Health 20, 1423–1424.
Chen, D.L., 2012. The control study of modified electroconvulsive therapy in treatment-refractory schizophrenia (In Chinese). Xinjiang Med. J. 42, 57–60.
Chen, Y.F., 2009. Electroconvulsive Therapy (In Chinese). China patent CN1230885.
Correll, C.U., Rubio, J.M., Inczedy-Farkas, G., Birnbaum, M.L., Kane, J.M., Leucht, S., 2017. Efficacy of 42 pharmacologic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. JAMA Psychiatry 74, 675–684.
Du, Z.H., Li, F.M., Liu, S.P., 2011. Efficacy and safety of clozapine combined electroconvulsive therapy in the treatment of refractory schizophrenia (In Chinese). Med. J. Chin. People's Health 23 (3056), 115.
Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.
Ferentinos, P.P., Kontaxakis, V.P., 2003. Treatment-resistant schizophrenia. Psychiatriki 14, 263–286.
Gerretsen, P., Diaz, P., Mamo, D., Kavanagh, D., Menon, M., Pollock, B.G., et al., 2011. Transient insight induction with electroconvulsive therapy in a patient with refractory schizophrenia: a case report and systematic literature review. J. ECT 27, 247–250.
Havaki-Kontaxaki, B.J., Ferentinos, P.P., Kontaxakis, V.P., Paplos, K.G., Soldatos, C.R., 2006. Concurrent administration of clozapine and electroconvulsive therapy in clozapine-resistant schizophrenia. Clin. Neuropharmacol. 29, 52–56.
Higgins, J.P., Green, S., 2008. Cochrane handbook for Systematic Reviews of Interventions. Wiley Online Library.
Howes, O.D., McCutcheon, R., Agid, O., de Bartolomeis, A., van Beveren, N.J., Birnbaum, M.L., et al., 2017. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. Am. J. Psychiatr. 174, 216–229.
Husni, M., Haggarty, J., Peat, C., 1999. Clozapine does not increase ECT-seizure duration. Canadian Journal of Psychiatry. Rev. Canad. Psychiatr. 44, 190–191.
Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., et al., 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Contr. Clin. Trials 17, 1–12.
Kales, H.C., Dequardo, J.R., Tandon, R., 1999. Combined electroconvulsive therapy and clozapine in treatment-resistant schizophrenia. Prog. Neuro Psychopharmacol. Biol. Psychiatr. 23, 547–556.
Kane, J., Honigfeld, G., Singer, J., Meltzer, H., 1988. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch. Gen. Psychiatr. 45, 789–796.
Kane, J.M., Correll, C.U., 2016. The role of clozapine in treatment-resistant schizophrenia. JAMA Psychiatry 73, 187–188.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative Syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.
Kho, K.H., Blansjaar, B.A., de Vries, S., Babuskova, D., Zwinderman, A.H., Linszen, D.H., 2004. Electroconvulsive therapy for the treatment of clozapine nonresponders suffering from schizophrenia–an open label study. Eur. Arch. Psychiatr. Clin. Neurosci. 254, 372–379.
Kittsteiner Manubens, L., Lobos Urbina, D., Aceituno, D., 2016. Is electroconvulsive therapy effective as augmentation in clozapine-resistant schizophrenia? Medwave 16 e6577.
Kupchik, M., Spivak, B., Mester, R., Reznik, I., Gonen, N., Weizman, A., et al., 2000. Combined electroconvulsive-clozapine therapy. Clin. Neuropharmacol. 23, 14–16.
Kurian, S., Tharyan, P., Jacob, K.S., 2005. Combination of ECT and clozapine in drug-resistant schizophrenia. Indian J. Psychiatr. 47, 245.
Lally, J., Tully, J., Robertson, D., Stubbs, B., Gaughran, F., MacCabe, J.H., 2016. Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: a systematic review and meta-analysis. Schizophr. Res. 171, 215–224.
Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., et al., 2013. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 382, 951–962.
Lewis, S.W., Barnes, T.R., Davies, L., Murray, R.M., Dunn, G., Hayhurst, K.P., et al., 2006. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr. Bull. 32, 715–723.
Liu, Q.Y., 2013. The clinical analysis of clozapine combined MECT in the treatment of refractory schizophrenia (In Chinese). Yiayao Qianyan 7, 199–200.
Liu, R.G., Li, H., Li, M., Gao, Y., 2015. Efficacy and safety of electroconvulsive therapy in the treatment of refractory schizophrenia (In Chinese). Guide. China Med. 13, 69.
Lou, Y.M., Xu, B.F., Li, X.F., 2013. Efficacy of clozapine combined MECT in the treatment of refractory schizophrenia (In Chinese). China J. Pharmaceut. Econ. 233–234.
Masiar, S.J., Johns, C.A., 1991. ECT following clozapine. Br. J. Psychiatry 158, 135–136.
Masoudzadeh, A., Khalilian, A.R., 2007. Comparative study of clozapine, electroshock and the combination of ECT with clozapine in treatment-resistant schizophrenic patients. Pakistan J. Biol. Sci. 10, 4287–4290.
McEvoy, J.P., Lieberman, J.A., Stroup, T.S., Davis, S.M., Meltzer, H.Y., Rosenheck, R.A., et al., 2006. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am. J. Psychiatr. 163, 600–610.
Meltzer, H.Y., 1992. Dimensions of outcome with clozapine. Br. J. Psychiatry 46–53.
Meltzer, H.Y., Bastani, B., Kwon, K.Y., Ramirez, L.F., Burnett, S., Sharpe, J., 1989. A prospective study of clozapine in treatment-resistant schizophrenic patients. I. Preliminary report. Psychopharmacology 99, S68–S72.
Meltzer, H.Y., Okayli, G., 1995. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. Am. J. Psychiatr. 152, 183–190.
Miyamoto, S., Jarskog, L.F., Fleischhacker, W.W., 2015. Schizophrenia: when clozapine fails. Curr. Opin. Psychiatr. 28, 243–248.
Nielsen, J., Correll, C.U., Manu, P., Kane, J.M., 2013. Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided? J. Clin. Psychiatr. 74, 603–613 quiz 13.
Nielsen, J., Young, C., Ifteni, P., Kishimoto, T., Xiang, Y.T., Schulte, P.F., et al., 2016. Worldwide differences in regulations of clozapine use. CNS Drugs 30, 149–161.
Overall, J.E., Beller, S.A., 1984. The Brief Psychiatric Rating Scale (BPRS) in geropsychiatric research: I. Factor structure on an inpatient unit. J. Gerontol. 39, 187–193.
Petrides, G., Malur, C., Braga, R.J., Bailine, S.H., Schooler, N.R., Malhotra, A.K., Kane, J.M., Sanghani, S., Goldberg, T.E., John, M., Mendelowitz, A., 2015. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. Am. J. Psychiatr. 172 (1), 52–58.
Porcelli, S., Balzarro, B., Serretti, A., 2012. Clozapine resistance: augmentation strategies. Eur. Neuropsychopharmacol 22, 165–182.
Remington, G., Lee, J., Agid, O., Takeuchi, H., Foussias, G., Hahn, M., et al., 2016. Clozapine's critical role in treatment resistant schizophrenia: ensuring both safety and use. Expet Opin. Drug Saf. 15, 1193–1203.
Safferman, A.Z., Munne, R., 1992. Combining clozapine with ECT. Convuls Ther. 8, 141–143.
Samara, M.T., Dold, M., Gianatsi, M., Nikolakopoulou, A., Helfer, B., Salanti, G., et al., 2016. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: a network meta-analysis. JAMA Psychiatr. 73, 199–210.
Siskind, D., McCartney, L., Goldschlager, R., Kisely, S., 2016. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br. J. Psychiatry 209, 385–392.
Siskind, D., Siskind, V., Kisely, S., 2017. Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. Can. J. Psychiatr.. Rev. Canad. Psychiatr. 62, 772–777.

Sommer, I.E., Begemann, M.J., Temmerman, A., Leucht, S., 2012. Pharmacological augmentation strategies for schizophrenia patients with insufficient response to clozapine: a quantitative literature review. Schizophr. Bull. 38, 1003–1011.

Taipale, H., Mehtala, J., Tanskanen, A., Tiihonen, J., 2017. Comparative effectiveness of antipsychotic drugs for rehospitalization in schizophrenia-a nationwide study with 20-year follow-up. Schizophr. Bull. https://doi.org/10.1093/schbul/sbx176.

Taylor, D.M., Smith, L., Gee, S.H., Nielsen, J., 2012. Augmentation of clozapine with a second antipsychotic - a meta-analysis. Acta Psychiatr. Scand. 125, 15–24.

Tharyan, P., Adams, C.E., 2005. Electroconvulsive therapy for schizophrenia. Cochrane Database Syst. Rev. CD000076.

Tiihonen, J., Haukka, J., Taylor, M., Haddad, P.M., Patel, M.X., Korhonen, P., 2011. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am. J. Psychiatr. 168, 603–609.

Tiihonen, J., Lonnqvist, J., Wahlbeck, K., Klaukka, T., Niskanen, L., Tanskanen, A., et al., 2009. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet 374, 620–627.

Tiihonen, J., Mittendorfer-Rutz, E., Majak, M., Mehtala, J., Hoti, F., Jedenius, E., et al., 2017. Real-World effectiveness of antipsychotic treatments in a nationwide cohort of 29823 patients with schizophrenia. JAMA Psychiatry 74, 686–693.

Trikalinos, T.A., Churchill, R., Ferri, M., Leucht, S., Tuunainen, A., Wahlbeck, K., et al., 2004. Effect sizes in cumulative meta-analyses of mental health randomized trials evolved over time. J. Clin. Epidemiol. 57, 1124–1130.

Veerman, S.R., Schulte, P.F., Begemann, M.J., de Haan, L., 2014. Non-glutamatergic clozapine augmentation strategies: a review and meta-analysis. Pharmacopsychiatry 47 (7), 231–238.

Veerman, S.R.T., Schulte, P.F.J., de Haan, L., 2017. Treatment for negative symptoms in schizophrenia: a comprehensive review. Drugs 77, 1423–1459.

Vermeulen, J.M., van Rooijen, G., van de Kerkhof, M.P.J., Sutterland, A.L., Correll, C.U., de Haan, L., 2018. Clozapine and long-term mortality risk in patients with schizophrenia: a systematic review and meta-analysis of studies lasting 1.1-12.5 years. Schizophr. Bull. https://doi.org/10.1093/schbul/sby052.

Wan, J.G., Xie, Y., Hu, S.M., Yu, X.N., Yang, B., Zhang, Y.M., et al., 2009. Efficacy of different course of modified electro-convulsive therapy on treatment-refracted schizophrenia (In Chinese). J. Neurosci. Ment. Health 9, 503–505.

Wang, W., Pu, C., Jiang, J., Cao, X., Wang, J., Zhao, M., et al., 2015. Efficacy and safety of treating patients with refractory schizophrenia with antipsychotic medication and adjunctive electroconvulsive therapy: a systematic review and meta-analysis. Shanghai Arch Psychiatr. 27, 206–219.

Wang, Z.H., Ling, Y.X., Xia, Z., 2011. Modified electroconvulsive therapy in the treatment of refractory schizophrenia (In Chinese). J. Clin. Psychiatr. 21, 252–254.

Weiner, R.D., 2008. The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging: a Task Force Report of the American Psychiatric Association. American Psychiatric Pub.

Xia, D.X., 2016. Clinical observation on MECT combined with clozapine for refractory schizophrenia (In Chinese). China Health Stand. Manag. 7, 113–114.

Xiang, Y.T., Kato, T.A., Kishimoto, T., Ungvari, G.S., Chiu, H.F., Si, T.M., Yang, S.Y., Fujii, S., Ng, C.H., Shinfuku, N., 2017. Comparison of treatment patterns in schizophrenia between China and Japan (2001-2009). Asia Pac. Psychiatr. 9 (4), 1–7.

Xiong, H., Liu, H.X., 2015. Clinical observation of MECT combined with clozapine for refractory schizophrenia (In Chinese). Sichuan Ment. Health 28, 348–350.

Yang, K.J., Liu, T.B., Yang, H.C., Gao, H., Wu, D.H., Feng, Z., et al., 2005. A comparative study of MECT combined with excitement aggressive behavior treatment on refractory schizophrenia (In Chinese). Med. J. Chin. People's Health 17, 485–486.

Yu, S.J., Liu, X.F., Liu, Y.Y., Gong, S.G., 2015. Modified electroconvulsive therapy in the treatment of refractory schizophrenia with negative symptoms (In Chinese). China Modern Doctor 53, 89–91 5.

Zeng, X.M., Liao, Y., 2010. Comparative study of clozapine versus clozapine combined with MECT in the treatment of refractory schizophrenia (In Chinese). Shanghai Arch. Psychiatr. 22, 95–96 114.

Zhang, S.Y., 2017. The Efficacy and Safety of MECT for Treatment-resistant Schizophrenia (In Chinese). Bao Jian Wen Hui, pp. 67.

Zhang, Y.J., Liu, Q., Hu, Y., Zhou, L.G., 2010. Effects of modified electroconvulsive therapy combined with clozapine in patients with treatment-refractory schizophrenia (In Chinese). Chin. Ment. Health J. 24, 440–444.

Zhang, Y.Y., Sun, Y.J., Lin, Z.H., Zhang, Q., 2011. A comparative study of clozapine combined electroconvulsive therapy in the treatment of refractory schizophrenia (In Chinese). J. Psychiatr. 24, 124–126.

Zhao, Y.H., Li, J., Wu, Y.C., Hu, J.Y., 2012. A comparative study of clozapine versus clozapine combined with MECT in the treatment of refractory schizophrenia (In Chinese). Med. J. Chin. People's Health 24, 2859–2861.

Zheng, W., Cao, X.L., Ungvari, G.S., Xiang, Y.Q., Guo, T., Liu, Z.R., et al., 2017. Electroconvulsive therapy added to non-clozapine antipsychotic medication for treatment resistant schizophrenia: meta-analysis of randomized controlled trials. PLoS One 11 e0156510.