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Augmentation strategies for clozapine resistance: a systematic review and meta-analysis

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Review Article

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Abstract

Background: Several augmentation strategies have been used to improve symptomatology in patients not adequately responding to clozapine. Several randomised controlled trials (RCTs) have evaluated the efficacy of different strategies to augment clozapine. This systematic review and meta-analysis reviewed the available RCTs that have evaluated the clinical efficacy of various pharmacological agents, non-pharmacological strategies (occupational therapy, cognitive behaviour therapy), and somatic treatment [electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation, etc.)] as augmenting agents to clozapine. *Methods:* Data were extracted using standard procedures, and risk of bias was evaluated. Effect sizes were computed for the individual studies. *Results:* Forty-five clinical trials were evaluated. The pooled effect size for various antipsychotic medications was 0.103 (95% CI: 0.288–0.493, $p < 0.001$); when the effect size was evaluated for specific antipsychotics for which more than one trial was available, the effect size for risperidone was −0.27 and that for aripiprazole was 0.57. The effect size for lamotrigine was 0.145, and that for topiramate was 0.392. The effect size for ECT was 0.743 (CI: 0.094–1.392). Risk of bias was low (mean Jadad score – 3.93). Largest effect sizes were seen for mirtazapine (effect size of 5.265). Most of the studies can be considered underpowered and limited by small sample sizes. *Conclusions:* To conclude, based on the findings of the present systematic review and meta-analysis, it can be said that compared to other treatment strategies, clozapine non-responsive patients respond maximum to mirtazapine followed by ECT.

Summation

- The available evidence suggests that electroconvulsive therapy is one of the most efficacious treatment strategies, in terms of augmentation of clozapine in patients with schizophrenia.
- In terms of augmentation with antipsychotics, available evidence suggests aripiprazole be superior to other antipsychotic agents.
- Evidence for augmentation with other agents is limited.

Considerations

- There are limited numbers of studies that have evaluated the efficacy of various treatment strategies in patients with schizophrenia responding poorly to clozapine.
- Most of the studies were considered underpowered and limited by small sample sizes.
- There is a need to expand the data by designing better quality studies.

Introduction

About 30% of patients with schizophrenia fulfil the criteria of treatment-resistant schizophrenia (TRS) (i.e., fail to respond to two adequate trials of antipsychotics) (Souza *et al.*, 2010; Porcelli *et al.*, 2012). For patients with TRS, clozapine is considered the mainstay of treatment (Šagud, 2015; Leung *et al.*, 2019). Evaluation of data of patients with TRS suggests that 30–70% of patients fail to respond to clozapine (Taylor *et al.*, 2000; De Berardis *et al.*, 2019; Roerig, 2019; Kudva & Gupta, 2016). This sub-group of patients are termed 'clozapine non-responders' or 'clozapine-resistant' (Souza *et al.*, 2010; Barber *et al.*, 2017) or having 'ultra-resistant' schizophrenia (Porcelli *et al.*, 2012; Elkis and Meltzer, 2007). These patients are challenging to manage and often lead to frustration among the clinicians. Although the available treatment guidelines suggest multiple treatment options for this sub-group of patients, the evidence for various suggested options is meagre.

The treatment strategies which have been evaluated for this group of patients include augmentation of clozapine with a second antipsychotic medication, mood stabiliser, antidepressant, other groups of medications such as memantine and glycine, electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), Occupational therapy, and cognitive behaviour therapy (CBT) (Grover & Sahoo, 2019). A few reviews have also evaluated the data for the use of these treatments in clozapine non-responders (Barber *et al*., 2017; Buchanan *et al*., 2010; Wang *et al*., 2018; Barbui *et al*., 2009; Wagner *et al*., 2019). There are specific studies on intervention modalities like antiepileptic drugs and second-generation antipsychotics (Zheng *et al*., 2017; Bartoli *et al*., 2019). The most recent meta-analysis on the topic was published in 2019 (Wagner *et al*., 2019). In a recent literature review, authors reported the identification of 21 reviews and meta-analyses, which have evaluated the evidence for clozapine augmentation or combination strategies. This review showed that the maximum number of trials included in any meta-analysis was 46 in numbers (Siskind *et al*., 2018). One of the meta-reviews reviewed the data from 21 reviews and meta-analyses by using the Scottish Intercollegiate Guidelines Network (SIGN) criteria to grade the available evidence to the four different levels and concluded that none of the treatment strategies met the grade A criteria (Wagner *et al*., 2019; Harbour & Miller, 2001). However, the combination of clozapine with first- or second-generation antipsychotics, augmentation of clozapine with ECT for persistent positive symptoms, and use of clozapine with certain antidepressants (fluoxetine, duloxetine, citalopram) for persistent negative symptoms were reported to have grade B level evidence (Wagner *et al*., 2019; Harbour & Miller, 2001). The evidence for augmentation of clozapine with lithium and anticonvulsants, glutamatergic agents, rTMS, tDCS, or CBT met grades C–D criteria only. Many of the previous meta-analyses and reviews have not addressed the risk of bias adequately, and all of these have not included studies evaluating the efficacy of non-pharmacological measures like CBT and occupational therapy in the meta-analysis. It is important that evidence-based approach for different augmentation strategies, the quality of evidence for each specific strategy needs to be analysed thoroughly, and the risk of bias needs to be documented separately. In this background, this systematic review and meta-analysis aimed to assess the evidence for augmentation of clozapine with various strategies and to assess the risk of bias in randomised controlled trials (RCTs) in patients not showing adequate response to clozapine.

Methods

Search strategy

For the identification of relevant literature, electronic searches were done using Google Scholar, PubMed and Science Direct, and Scopus databases. The keywords included clozapine, augment*, resistan*, non-respon*, schizophrenia, psychosis, clozapine resistant, and clozapine refractory in various permutations and combinations. Initially, the word 'clozapine' was combined with each of these terms (e.g., augment*), and then the terms were substituted one after the other, with clozapine remaining as a search term. In the later searches, permutations and combinations of more than two words were used. The searches were carried out in April 2022. Additional literature was identified from the cross-references and through hand searches.

Selection of studies

Placebo-controlled RCTs published in English-language peer-reviewed journals that evaluated the efficacy/effectiveness of interventions in patients with clozapine resistance were included. The studies which did not present separate data for intervention were excluded. Similarly, studies for which effect sizes could not be computed with the available data were also excluded.

Data extraction

Abstracts of the identified studies were sifted through and the full texts of the papers were obtained. The extracted data were coded independently by two investigators (SS and SS). Information pertaining to study characteristics, demographic characteristics, and clinical details was extracted. Discrepancies between the investigators were resolved after a mutual discussion, involving the third author (SG) and a re-evaluation of the published paper.

Risk of bias

The Jadad scale (Jadad *et al*., 1996), which has good validity and reliability (Clark *et al*., 1999), is a five-point scale for assessing the quality of RCTs and was used to quantify the risk of bias. The rating is done based on reporting of randomisation, blinding, and reporting of withdrawals and drop-outs.

Statistical analysis

Effect sizes and 95% confidence intervals (CI) for the efficacy of the intervention were determined. If any study reported more than one outcome measure, then the primary outcome measure or the measure considered to be most clinically relevant was used to calculate effect size. If any study did not explicitly mention a primary efficacy variable, then the proportion of patient's improved or the improvement in the positive psychotic symptoms was taken for computation of effect sizes. Hedges g test, which gives a robust measure for both categorical and continuous data, was used to calculate effect sizes. The logit method was used for determining the effect size and confidence intervals for the dichotomous variables.

The obtained effect sizes were entered into OpenMetaAnalyst software for the computation of standardised mean differences. Random effects models were used due to the heterogeneity of studies. The standardised mean differences and effect sizes were computed for each of the following categories of interventions: antipsychotics, antidepressants, mood stabilisers and anticonvulsants, memantine, amino acids and alternate treatments, ECT, rTMS, and other interventions. For assessing the heterogeneity, I^2 test was used. Forest plots were constructed to represent the studies graphically.

Results

Initial search of the literature showed 6271 studies. Abstracts of all these studies were screened for eligibility and 60 abstracts were considered to be relevant. We excluded the articles which reported findings of the meta-analysis, open-label studies, retrospective studies, review articles, treatment guidelines, on-going clinical trials/ study protocols, non-placebo-controlled comparative studies, articles published in languages other than English, case series, case reports, and those articles for which full texts were not available. An attempt was made to assess the full text of all these studies. Unfortunately, we could not access the full texts of six of the articles involving valproate augmentation. Of the remaining 54 studies, 9

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could not be included, as the data were insufficient to calculate the effect sizes. After excluding all these studies, we were left with 45 placebo-controlled RCTs included in the meta-analysis.

Antipsychotics

The antipsychotics that have been commonly evaluated as the augmenting agent to clozapine include risperidone, aripiprazole, haloperidol, sulpiride, and ziprasidone, with the maximum number of studies on risperidone (Table 1 and Supplementary Figure 1). The sample sizes across different studies ranged from 6 to 207, and the duration of trials ranged from 8 weeks to 24 weeks. The most commonly used primary outcome measure in these trials was Brief Psychiatric Rating Scale (BPRS) or Positive and Negative Syndrome Scale (PANSS). When the meta-analysis of these trials was carried out, it was seen that overall antipsychotics were not more effective than placebo (standardized mean difference = 0.103, 95% CI −0.288 to 0.493, $p < 0.001$, $I^2 = 85\%$). This was mainly due to negative findings from one of the studies on risperidone. The pooled effect size for the five risperidone trials was −0.274 (95% CI −1.261 to 0.714, $I^2 = 91\%$). Similarly, the pooled effect size for the three aripiprazole trials was 0.574 (95% CI from 0.112 to 1.037, $I^2 = 67\%$).

Mood stabilisers

In terms of mood stabilisers, studies have evaluated lamotrigine, topiramate, and valproate as the augmenting agents in the descending order of frequency (Table 2 and Supplement Figure 2). Outcome measures used in these studies were PANSS and clinician-rated improvement status. The sample sizes in these studies have ranged from 4 to 80, and the duration of trials varied from 10 to 24 weeks. Overall, when compared to placebo, the mood stabilisers and anticonvulsants were found to be more effective (standardized mean difference = 0.265, 95% CI 0.016–0.515, $p = 0.194$, $I^2 = 28\%$). The pooled effect size for lamotrigine was 0.145 (95% CI −0.154 to 0.445, $I^2 = 0\%$), and that for topiramate was 0.392 (95% CI −0.045 to 0.830, $I^2 = 56\%$).

Antidepressants

In terms of antidepressants, only three RCTs have evaluated antidepressants for augmentation of clozapine (Supplement Table 1, Supplement Figure 3). While one study with mirtazapine and another with duloxetine showed significant improvement in BPRS and PANSS scores, respectively, another study evaluated fluoxetine and did not find a significant change in BPRS positive symptoms score. Overall, antidepressants were found to be conclusively better than placebo (standardized mean difference = 2.062, 95% CI 0.187–3.938, $p < 0.001$, $I^2 = 92.1\%$). However, it must be remembered that the analysis was limited to only three studies. Among the antidepressant, largest effect size was seen for mirtazapine.

Other agents

Few studies have evaluated memantine, amino acids, and alternate treatments for the augmentation of clozapine (Table 3 and Supplementary Figure 4). Memantine and glycine were evaluated in two trials, while D-cycloserine, D-serine, sarcosine, ampakine CX516, and ginkgo biloba were evaluated by one study each. The sample sizes for these studies ranged from 16 to 52, and the duration of the trials ranged from 4 weeks to 13 weeks. PANSS, BPRS, and Scale for Assessment of Negative Symptoms (SANS) were used to evaluate the outcome. These interventions were not seen to be conclusively effective (standardized mean difference = 0.378, 95% CI −0.027 to 0.784, $p = 0.006$, $I^2 = 57\%$). The two studies of memantine had a pooled effect size of 0.948 (95% CI −1.689 to 3.584, $I^2 = 94\%$), while the three studies of glycine had an effect size of 0.118 (95% CI −0.399 to 0.635, $I^2 = 0\%$).

Somatic and psychosocial treatments

Some RCTs have evaluated ECT, rTMS, occupational therapy, and CBT (Table 4 and Supplementary Figure 5). The duration of these interventions has ranged from 10 days (for rTMS) to 6 months (for occupational therapy). Two studies used BPRS, two used PANSS, and the occupational therapy trial used the Scale for Interactive Observation in Occupational Therapy as the outcome measure. Among these RCTs, trials evaluating ECT, one out of two studies of rTMS, and trials of occupation therapy and CBT showed that these active interventions were more effective than the control conditions. Overall, these interventions were seen to be effective (standardized mean difference = 0.781, 95% CI 0.401–1.161, $p = 0.581$, $I^2 = 0\%$).

The various specific interventions are presented in Supplementary Figure 6 which shows the sub-group analysis which suggests that sulpiride, ziprasidone, mirtazapine, D-cycloserine, ampakine X516, ECT, occupation therapy, and CBT are effective (the confidence intervals did not span zero) augmentation strategies in patients not responding to clozapine.

Exploratory analyses were conducted to see whether there was an effect of the study duration, sample size, or outcome measure on the efficacy. The sample size (tau = 0.212, $p = 0.041$) had some relationship with the effect size (i.e. larger studies tended to have smaller effect size, implying the possibility of file drawer effect). The type of outcome measure (coded into BPRS, PANSS, and others) did not relate to the effect sizes.

Funnel plot of all included studies

The Egger test of asymmetry of all the studies suggested no significant evidence of publication bias ($B = 0.569$, $p = 0.209$) (Supplementary Figure 7). The visual inspection of the studies does suggest the possibility of publication bias.

Risk of bias

When the risk of bias was evaluated by using Jadad score, the scores ranged from 1 to 5 with a median of 4 (mean of 3.93, mode 5) (Supplementary Table 2). Only six studies had Jadad score of less than 3 and none had a score of 0. The maximum number of studies had used intention to treat analysis, while 15 studies ($n = 15$) had not relied on such statistical procedures or had not mentioned using statistical methods to estimate intention to treat (Muscatello *et al.*, 2011a; Mossaheb *et al.*, 2006; Zoccali *et al.*, 2007; Vayısoğlu *et al.*, 2013; Muscatello *et al.*, 2011b; Behdani *et al.*, 2011; Tiihonen *et al.*, 2005; Buchanan *et al.*, 1996; Zoccali *et al.*, 2004; Veerman *et al.*, 2016; Potkin *et al.*, 1999; Evins *et al.*, 2000; Diaz *et al.*, 2005; Goff *et al.*, 2001; Dean *et al.*, 2015).When the association of the year of publication and risk of bias (measured with Jadad scale) were evaluated, a statistically significant correlation (Kendall tau correlation of 0.312, $P = 0.008$) was seen.

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Table 1. Trials of antipsychotic augmentation of clozapine

References	Sample size	Mean age in years	Gender distribution	Definition of clozapine resistance used	Duration in weeks	Outcome measure	Effect size	Confidence intervals Lower	Confidence intervals Upper
Risperidone									
Josiassen *et al.* (2005)	40	Clz/Ris: 40.8; Clz/P: 39.9	Ris: M – 19, F – 1; P: M – 16, F – 4	Lack of satisfactory clinical response to a trial of clozapine for 3 or more months with at least 600 mg/day or a plasma drug level of 350 ng/ml or higher). Presence of persistent psychotic symptoms, as evidenced by either a total score of at least 45 on the BPRS or a rating of moderately ill (4 or more) on at least two of the four BPRS positive symptom items	12	BPRS	0.870	−0.208	1.948
Yağcioğlu *et al.* (2005)	30	Ris: 35.3 ± 10.8; P: 31.2 ± 6.9	Ris: M – 11, F – 3; P: M – 9, F – 7	PANSS score of at least 72, despite receiving clozapine 300–900 mg/day for at least 6 months	6	PANSS	−3.300	−4.401	−2.199
Honer *et al.* (2006)	68	Ris: 39.4; P: 34.9	Ris: M – 25; P: M – 25	PANSS score of at least 80, despite receiving clozapine at least 400 mg/day (lower doses in case the patient is not able to tolerate) for at least 12 weeks	8	PANSS	−0.020	−0.496	0.455
Freudenreich *et al.* (2007)	24	42.3	M: 87.5% (of total patients in both arms)	Clozapine monotherapy for at least 6 months, at a stable dose for at least 8 weeks and with clozapine plasma levels of at least 200 ng/mL (or lower levels in case the patient is not able to tolerate)	6	PANSS	0.447	−0.365	1.260
Weiner *et al.* (2010)	69	Ris: 48.3; P: 44.1	Ris: M – 19, F – 11; P: M – 25, F – 9	Clozapine treatment for 6 months on a dose that produced a clozapine plasma level of 350 ng/ml or a clozapine + norclozapine plasma level of 450 ng/ml	16	BPRS	0.347	−0.119	0.812
Sulpiride/Amisulpride									
Shiloh *et al.* (1997)	28	Sul: 40.3; P: 37.1	Sul: M – 11, F – 5; P: M – 8, F – 4	Partial and unsatisfactory response (BPRS score of at least 25 and inability to function as an outpatient) to at least 12 weeks of clozapine treatment in an adequate dose	10	BPRS	0.832	0.044	1.602
Barnes *et al.* (2017)	68	Ami: 39; P: 40	Ami: M – 24, F – 35; P: M – 23, F – 33	Treatment for at least 12 weeks at a stable dose of at least 400 mg/day (lower dose in case of intolerance) and a total score of ≥80 at baseline on the PANSS; a clinical global impression (CGI) score of ≥4 ; a SOFAS score of ≤40	12	PANSS	−0.056	−0.532	0.419
Aripiprazole									
Chang *et al.* (2008)	62	Arip: 33.2 ± 8.2; P: 31.7 ± 7.4	Arip: M – 22, F – 7; P: M – 26, F – 6	Receiving clozapine for more than 1 year with at least 8 weeks at a stable dose of at least 400 mg/day with a BPRS total score of at least 35	8	BPRS	0.108	−0.395	0.611

(*Continued*)

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Table 1. (*Continued*)

References	Sample size	Mean age in years	Gender distribution	Definition of clozapine resistance used	Duration in weeks	Outcome measure	Effect size	Confidence intervals Lower	Confidence intervals Upper
Fleischhacker *et al.* (2010)	207	Arip: 37.6; P: 40.5	Arip: M – 68, F – 40; P: M – 66, F – 33	A stable dose of clozapine (200–900 mg/day) for at least 3 months without optimal control of symptoms and experienced weight gain of 2.5 kg while on clozapine	16	PANSS	0.826	0.542	1.110
Muscatello *et al.* (2011)	31	Arip: M – 31.9; P: 30.7	Arip: M – 8, F – 6; P: M – 9, F – 8	Presence of persistent positive and negative symptoms (BPRS score of at least 25) despite an adequate trial of clozapine	24	BPRS	0.732	0.092	1.372
Sertindole									
Nielsen *et al.* (2012)	50	Ser: 41.8, P: 42.7	Ser: M – 15; P: M – 15	Clozapine for at least 6 months at an optimised dose (minimum 150 mg/day) and at least having PANSS score of 65	12	PANSS	0.614	0.046	1.181
Pimozide									
Friedman *et al.* (2011)	53	Pim: 44.4; P: 45.5	Pim: M – 21, F – 4; P: M – 20, P – 8	Persistent positive psychotic symptoms characterised by PANSS scores of 4 or higher on at least two items from the positive subscale, a PANSS total score ≥60 and a CGI ≥4 on four consecutive assessments	12	PANSS	−0.279	−0.821	0.263
Ziprasidone									
Muscatello *et al.* (2014)	40	Zip: 36.5; P: 33.5	Zip: M – 5, F – 15; P: M – 8, P – 12	Presence of persistent positive and negative symptoms (BPRS score of at least 25) despite an adequate trial of clozapine	16	PANSS	0.603	−0.030	1.237
Haloperidol									
Mossaheb *et al.* (2006)	6	H: 32.5; P: 32.5	Not mentioned	Clozapine trial of at least 6–8 weeks in adequate dosage	10	PANSS	−1.075	−1.738	−0.412

BPRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Syndrome Scale; Ris: Risperidone; Ami: Amisulpride; Sul: Sulpiride; Pim: Pimozide; Ser: Sertindole; Arip: Aripiprazole; H: Haloperidol; Zip: Ziprasidone; M: Males; F: Females.

Discussion

Clozapine resistance poses a major clinical challenge to clinicians. Clinicians are always on the lookout for choosing an agent that can improve the clinical outcome of the patient. This systematic review and meta-analysis suggest that there are limited numbers of RCTs that have evaluated various agents among patients with clozapine resistance. It is evident from the data that most of these studies are of small sample size, with the largest study sample being of 487. Further, the limitation of the existing literature, which must be considered while interpreting the results of this systematic review and the meta-analysis, includes inconsistency in defining clozapine resistance. The definitions have varied significantly across different studies. Hence, findings of the present meta-analysis must be construed in this background.

One of the recent meta-analyses on the same topic included 46 RCTs, with searches in both Chinese and non-Chinese databases. In contrast, the present meta-analysis was limited to studies published in English only. However, when one compares the studies included in the current meta-analysis with this meta-analysis, there is only an overlap of 26 studies. We did not include 15 studies published in the Chinese language and we did not include another study, as it did not provide information separately for clozapine (Berk, 2014). Accordingly, the present meta-analysis provides broader details on the studies published in the English language.

When one evaluates the effect size of interventions, it is evident that the effect size for various antipsychotic medications was 0.103; however, when the effect size was evaluated for specific antipsychotics for which more than one trial was available, the effect size for risperidone was −0.274 (negative effect size primarily due to one study) (Yağcioğlu *et al.*, 2005) and that for aripiprazole was 0.574. The effect size for mood stabilisers was 0.265, with that for lamotrigine being 0.145, and that for topiramate being 0.392 (with either being not significantly better than placebo). The effect size for glycine was 0.118 and the effect size for ECT was 0.743. In general, it is suggested that effect size of 0.2 is considered to be small, 0.5 is considered to be medium, and 0.8 is considered to

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Table 2. Trials of mood stabiliser and anticonvulsant augmentation of clozapine

References	Sample size	Mean age in years	Gender distribution	Definition of clozapine resistance used	Duration in weeks	Outcome measure	Effect size	Confidence intervals Lower	Confidence intervals Upper
Lamotrigine									
Tiihonen *et al.* (2003)	34	Lamo: 38.2; P: 38.3	Data not available	Non-satisfactory response to clozapine of at least 6 months	14	PANSS	0.175	−0.500	0.850
Zoccali *et al.* (2007)	60	Lamo: 32.5; P: 30.2	Lamo: M – 15, F – 11; P: M – 13, F – 12	Presence of persistent positive and negative symptoms (BPRS score of at least 25) despite an adequate trial of clozapine	24	PANSS	−0.239	−0.747	0.269
Vayısoğlu *et al.* (2013)	34	Lamo: 40.5; P: 41.2	Lamo: M – 10, F – 7; P: M – 13, F – 4	PANSS score of at least 70 and CGI score of at least 3, receiving 150–900 mg/day of clozapine treatment for at least a year, with a stable dose in the previous month	12	PANSS	0.402	−0.278	1.081
Kremer *et al.* (2004)	38	Lamo: 44.1; P: 42.3	Lamo: M – 17, F – 8; P: M – 6, P – 7	Not mentioned specifically	10	PANSS	0.546	−1.450	2.542
Goff *et al.* (2007)	42	Overall: 41.6 ± 10.6	74.3% subjects were males	Serum clozapine concentration of at least 350 ng/mL or maintained on at least 300 mg/day of clozapine	12	PANSS	0.433	−0.179	1.045
Topiramate									
Muscatello *et al.* (2011)	43	T: 32.3 ; P: 31.5	T: M – 14, F – 5; P: M – 17, P – 7	Presence of persistent positive and negative symptoms (BPRS score of at least 25) despite an adequate trial of clozapine	24	PANSS	0.433	−0.176	1.042
Behdani *et al.* (2011)	80	T: 45.12; P: 46.93	T: M – 37, F – 3; P: 31, F – 9	Receiving at least 300 mg/day of clozapine	17	PANSS-P	−0.053	−0.491	0.386
Tiihonen *et al.* (2005)	26	T: 42.0 ± 11.4; P: 45.5 ± 14.4	Not mentioned	Non-satisfactory response to at least 4 months of clozapine treatment	12	PANSS	0.384	−0.206	0.974
Afshar *et al.* (2009)	32	T: 37.5; P: 38.1	T: M – 9; P: M – 11	Non-satisfactory response to clozapine at a maximum tolerable dose of ≥100 mg/day in the previous 2 months	8 weeks	PANSS	1.057	0.317	1.797

PANSS: Positive and Negative Syndrome Scale; PANSS-P: Positive symptom subscale of PANSS; T: Topiramate; Lamo: Lamotrigine.

be large. Accordingly, it can be said that among the various interventions, the effect size is highest for mirtazapine, followed by D-cycloserine. However, it is important to note that these were based on single small sample size study. Accordingly, the findings must be interpreted in this background. The previous meta-analysis suggests that lamotrigine may be of some benefit among patients with clozapine resistance for positive symptoms and general psychopathology symptoms, but not for negative symptoms (Zheng *et al.*, 2017; Tiihonen *et al.*, 2009). Present meta-analysis provides further credence to these findings. The high effect size for ECT suggests that it should be preferred in patients not responding to clozapine if there are no contraindications for ECT. However, it is important to note that this is also based on a single study, but the sample size of this study was larger than that for mirtazapine and D-cycloserine. If we attempt to evaluate the efficacy of various agents as per the SIGN criteria, findings of the present study support the conclusion of the recent review of all the available systematic reviews and meta-analysis, which suggest that ECT has evidence of grade B (Wagner *et al.*, 2019). However, our meta-analysis contradicts the assertion that the level of evidence for anticonvulsants, that is, lamotrigine, is that of grade C or D (Wagner *et al.*, 2019).

Present meta-analysis shows that the addition of a second antipsychotic may not be useful in clozapine non-responders, though

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Table 3. Trials of memantine, amino acids, and alternate treatments for augmentation of clozapine

References	Medication	Sample size	Mean age in years	Gender distribution	Definition of clozapine resistance used	Duration in weeks	Outcome measure	Effect size	Confidence intervals Lower	Confidence intervals Upper
De Lucena *et al.* (2009)	Memantine	21	Mem: 34.6 ± 9.99; P: 34.73 ± 8.57	Mem: M- – 8, F-2; P: M – 11	Receiving clozapine for at least 10 years with partial remission of negative symptoms	12	BPRS	2.339	1.228	3.450
Veerman *et al.* (2016)	Memantine	52	42.35 ± 9.55 (overall mean)	75% males out of total participants	Lack of satisfactory response to clozapine therapy of at least 6 months with a clozapine plasma level above 350 ng/ml for at least 12 weeks or intolerability to achieve this threshold	12	PANSS	−0.353	−0.901	0.195
Potkin *et al.* (1999)	Glycine	19	12.4 ± 7.2 (overall mean)	Gly: M – 10, F – 2; P: M – 11, F – 1	Symptomatic despite being maintained on optimal doses of clozapine (range = 400–1200 mg/day) for several months	12	BPRS	0.457	−0.455	1.369
Evins *et al.* (2000)	Glycine	30	39 ± 7 (overall mean)	Not mentioned specifically	Inadequate response to a stable dose of clozapine for at least 4 weeks	8	PANSS	−0.076	−0.831	0.679
Diaz *et al.* (2005)	Glycine	12	39.5 ± 12.44 (overall mean)	M – 9, F – 3 (overall)	Partial or non-response to clozapine	28	PANSS	0.032	−1.100	1.163
Goff *et al.* (1999)	D-Cycloserine	10	40.4 ± 6.1 (overall mean)	All the 10 subjects were males	Subjects on stable dose of clozapine for at least 4 months	2	SANS	1.367	0.050	2.685
Tsai *et al.* (1999)	D-serine	20	Ser: 42.6 ± 3.6; P: 39.5 ± 5.5	Sex ratio in both arms was similar- 5:5 for placebo and 4:6 for serine	Inadequate response to stable doses of clozapine for at least 3 months before enrolment	6	PANSS- P	0.529	−0.363	1.421
Lane *et al.* (2006)	Sarcosine	20	Sar: 36.7 ± 10.1; P: 35.5 ± 6.6,	Sar: M – 7, F – 3; P: M – 7, F – 3	PANSS score of at least 70 and On constant clozapine doses for at least 3 months	6	PANSS	−0.292	−1.173	0.589
Goff *et al.* (2001)	AmpakineCX516	18	39.8 ± 10.5 (overall)	M – 16, F – 3 (overall)	Receiving mean daily clozapine dose of 406.6 ± 126.6 mg/day	4	PANSS	0.716	−0.291	1.724
Doruk *et al.* (2008)	*Ginkgo biloba*	42	G: 29.7 ± 4.8; P: 31.9 ± 5.2	G: M – 11, F – 9; P: M – 16, F – 6	Not mentioned specifically	12	BPRS	0.211	−0.396	0.818
Kelly *et al.* (2015)	Minocycline	50	Mino: 42.9 ± 4.2; P: 42.3 ± 11.0	Mino: M – 20; P: M – 18	Receiving at least 200 mg/day of clozapine for 6 months and had achieved a serum CLZ level of >350 ng/ml.		BPRS	1.098	−0.103	2.300
Freudenreich *et al.* (2009)	Modafinil	35	Mod: 44.2 ± 12.0; P: 46.4 ± 6.4	Mod: M – 15, F – 4; P: M – 12, F – 4	Receiving clozapine for at least 6 months, with a stable dose for at least 1 month	8	PANSS	−0.450	−1.640	0.740
Dean *et al.* (2015)	N-Acetyl cysteine	55	Not mentioned	Not mentioned	Not defined	24	PANSS Total	0.220	−2.970	3.410

BPRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Syndrome Scale; PANSS-P: Positive symptom subscale of PANSS; SANS: Scale for the assessment of negative symptoms; Mem: Memantine; Sar: Sarcosine; Ser: D-Serine; Gly: Glycine, G: Gingko Biloba; Mod: Modafinil; Mino: Minocycline; M: Males; F: Females.

Table 4. Trials of other interventions for augmentation of clozapine

References	Intervention	Sample size	Mean age in years	Gender distribution	Definition of clozapine resistance used	Duration	Outcome measure	Effect size	Confidence intervals lower	Confidence intervals upper
Petrides *et al.* (2015)	ECT	39	ECT: 35.7 ± 2.27; Only Clz: 42.7 ± 1.82	ECT: M – 15, F – 5; Only Clz: M – 13, F – 6	Presence of persistence of psychotic symptoms. Despite receiving clozapine for at least 12 weeks, at a blood level 350 ng/mL	8 weeks	BPRS	0.743	0.094	1.392
Rosa *et al.* (2007)	rTMS	11	rTIMS: 29.83 ± 8.40; Sham: 33.0 ± 12.08	rTIMS: M – 4, F – 2; Sham: M – 2, F – 3	Presence of persistent auditory hallucinations despite being on clozapine at least 350 mg/day for 6 months	10 days	PANSS	0.182	−1.007	1.372
De Jesus *et al.* (2011)	rTMS	17	rTIMS: 46 ± 9.84; Sham: 36.5 ± 6.36	11 (overall) rTMS: M – 5, F – 3; Sham: M – 7, F – 2	Experiencing auditory verbal hallucinations while treated with clozapine	20 days	BPRS	1.251	0.210	2.292
Buchain *et al.* (2003)	OT	26	OT: 33.71 ± 6.9; CG: 36.58 ± 6.6	OT: M – 9, F – 5; CG: M – 10, F – 2	Stable doses of clozapine with BPRS score of at least 45	6 months	EOITO	0.891	0.083	1.699
Barretto *et al.* (2009)	CBT	21	CBT-39.8 ± 7.7; BF-33.2 ± 12.4	CBT: M – 7, F – 5; BF: M – 4, F – 5	Receiving clozapine for at least 6 months without improvement of the psychotic symptom	21 week	PANSS	0.943	0.033	1.853
Morrison *et al.* (2018)	CBT	487	CBT-42.2 ± 10.7; TAU-42.8 ± 10.4	CBT: M – 176, F – 66; TAU: M – 173, F – 72	Persistent symptoms despite receiving clozapine at a stable dose of 400 mg or more (unless limited by tolerability) for at least 12 weeks	21 months	PANSS	−0.890	−3.320	1.550

OT: occupational therapy; CBT: cognitive behaviour therapy; BPRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Syndrome Scale; EOITO: Scale for Interactive Observation in Occupational Therapy; BF: Befriending; M: Males; F: Females; TAU: treatment as usual.

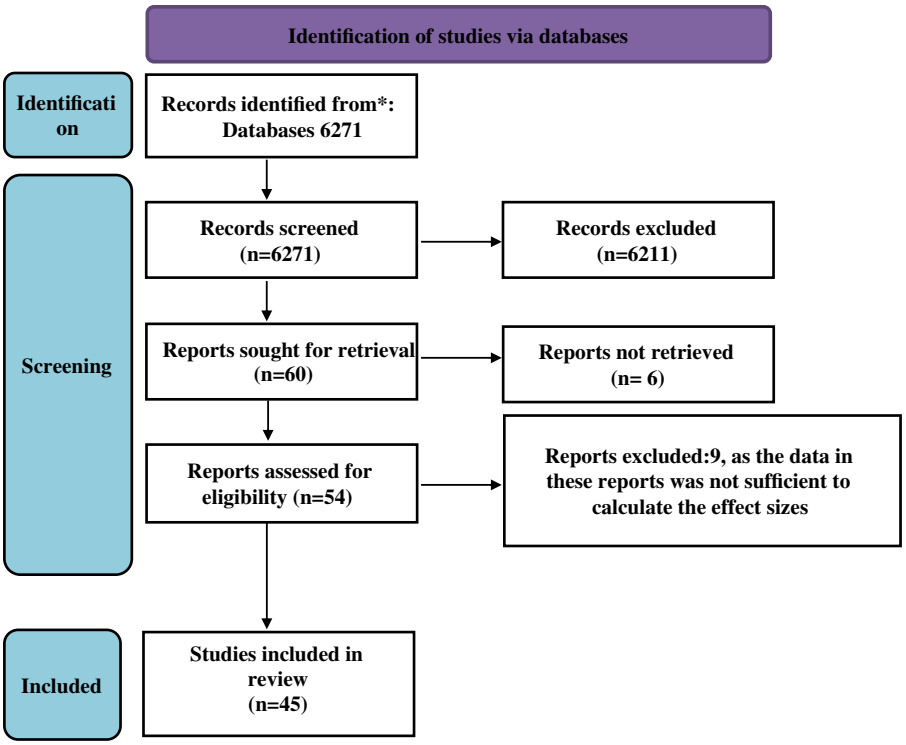

Fig. 1. Prisma flow diagram.

certain antidepressants may help. Some of the previous meta-analyses, (Barber *et al.*, 2017) which have also limited themselves to RCTs, suggest that in contrast to placebo, addition of second antipsychotic medication in patient with inadequate response to clozapine does not lead to significant improvement in positive symptoms, as suggested by small effect sizes in the present study, which were non-significant too. Further, the evidence from the available meta-analyses also offers a high degree of heterogeneity with minimal or no publication bias. Present meta-analysis and systematic review support the existing literature.

Several novel antipsychotics and other approaches are likely to be used in clozapine-resistant schizophrenia in the future. rTMS has been evaluated, and possibly other neuromodulation techniques may find considered for evaluation of clozapine-resistant cases. The adjunctive therapies may include approaches to reduce distress due to psychotic symptoms. In fact, the largest study for clozapine augmentation was on CBT. Assessment of outcomes has generally been done using PANSS and BPRS scales. Uniform application of these instruments and reporting their findings is likely to help maintain comparability across studies.

Findings of the present meta-analysis are limited by the existing literature. We could not include some RCTs, especially those involving valproate, due to non-availability and some other studies due to lack of data to calculate effect sizes. We have used the Jadad criteria for the assessment of the risk of bias, while other methods like Cochrane recommendations have become more popular now. The Egger's test may not have picked up publication bias due to low sample sizes. Additionally, we did not evaluate the inter-rater agreement during the search process.

To conclude, based on the findings of the present systematic review and meta-analysis, it can be said that ECT or antipsychotics maybe preferred over other treatment strategies, and if this is not feasible, then lamotrigine must be considered much before the use of other agents.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/neu.2022.30

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