Pharmacological Augmentation Strategies for Schizophrenia Patients With Insufficient Response to Clozapine: A Quantitative Literature Review

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Background. When schizophrenia patients have insufficient response to clozapine, pharmacological augmentation is often applied. This meta-analysis summarizes available evidence on efficacy of pharmacological augmentation of clozapine treatment in schizophrenia spectrum disorder. Methods. Only double-blind randomized controlled studies were included. Primary outcome measure was total symptom severity, and secondary outcome measures were subscores for positive and negative symptoms. Effect sizes were calculated from individual studies and combined to standardized mean differences (Hedges’s g). Results. Twenty-nine studies reporting on 15 different augmentations were included. Significant better efficacy than placebo on total symptom severity was observed for lamotrigine, citalopram, sulpiride, and CX516 (a glutamatergic agonist). The positive effect of lamotrigine disappeared after outlier removal. The other positive findings were based on single studies. Significantly better efficacy on positive symptom severity was observed for topiramate and sulpiride. The effect of topiramate disappeared after outlier removal. Results for sulpiride were based on a single randomized controlled trial. Citalopram, sulpiride, and CX516 showed better efficacy for negative symptoms than placebo, all based on single studies. Conclusions. Evidence for efficacy of clozapine augmentation is currently scarce. Efficacy of lamotrigine and topiramate were both dependent on single studies with deviating findings. The effect of citalopram, sulpiride, and CX516 were based on single studies. Thus, despite their popularity, pharmacological augmentations of clozapine are not (yet) demonstrated to be superior to placebo.

Key words: schizophrenia/augmentation/clozapine/resistant

Introduction

Although antipsychotic agents are effective in the majority of patients with schizophrenia, between one-fifth and one-third of patients have little, if any, benefit from them.1 Treatment of these patients has remained a persistent public health problem as medication-resistant patients are often highly symptomatic,2 have a severely reduced quality of life, and need extensive periods of hospital care.2 They also require a disproportionately high amount of the total health costs for schizophrenia.3,4

The landmark trial of Kane et al5 demonstrated superior efficacy for clozapine over other antipsychotic agents for this subgroup of medication-resistant patients, a finding that has now consistently been replicated.6-8 In order to optimize clozapine therapy, several studies have evaluated the relationship between clozapine blood levels and therapeutic response. Clozapine levels above 350-450 µg/ml are shown to be associated with superior treatment response than lower levels (reviewed by Schulte9). Although clozapine is considered the most efficient antipsychotic agent in refractory patients, as many as 40%-70% of these patients achieve only poor or partial response with it, even with adequate blood levels of clozapine.5,10-12 For these ultra-resistant patients, several treatment strategies can be followed, including psychotherapy,13 pharmacological augmentation,14 repetitive transcranial magnetic stimulation,15 or electroconvulsive therapy.16 Augmentation of clozapine with another pharmacological substance is used frequently in clinical practice, despite the paucity of evidence that adding a second drug will enhance antipsychotic properties.17-20 Some of the most frequently prescribed augmentation components are lithium, sodium valproate, benzodiazepines, various selective serotonin reuptake inhibitors (SSRIs), risperidone, haloperidol, and aripiprazole.21 Since clinicians quite routinely turn to pharmacological augmentation strategies when facing clozapine-resistant...
schizophrenia patients, a critical evaluation of the efficacy of pharmacological agents in augmenting clozapine treatment response is warranted.

There are numerous reports available regarding augmentation strategies in patients with poor or partial response to clozapine. Augmentation with conventional or atypical antipsychotics,22,23 various antidepressants,24,25 lithium,26 sodium valproate,27 carbamazepine,28 novel anticonvulsants,29 dopamine agonists,30 glutamate receptor agonists,31 mazindol,32 and omega-3 fatty acids33 have all been described as clozapine adjuncts in the treatment of resistant symptoms. The available literature addressing different augmentation strategies in clozapine-resistant patients seems promising at first glance because most reports suggest that therapeutic benefits can be gained.14,34–36 However, most studies are case reports, retrospective chart reviews, and small sampled uncontrolled trials. Such studies tend to produce a strong bias for positive results because negative reports in a case or a small sample are unlikely to be reported and/or published.37,38 In addition, the specific therapeutic response cannot be distinguished from placebo effects in uncontrolled studies. Meanwhile, there are only few randomized controlled trials (RCTs) available.

Perhaps as a result of the paucity of well-designed studies, expert guidelines have generally been reticent about augmentation strategies for clozapine-resistant patients.38,39 For example, the 2009 Schizophrenia Patient Outcomes Research Team has discussed adjunctive treatment strategies but argued that studies have failed to document sufficient efficacy to support a recommendation in patients with clozapine-resistant schizophrenia.40

Therefore, this study aims to review all double-blind randomized controlled studies available regarding the efficacy of pharmacological augmentation in clozapine-resistant patients, and perform meta-analyses on the efficacy of individual clozapine adjuncts when sufficient studies are available. By quantitatively summarizing the literature on clozapine augmentation strategies, this review aims to assess the efficacy of the different clozapine augmentation strategies in reducing persistent positive and negative symptoms of schizophrenia.

Methods

**Literature Search**

This meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) Statement.41 The protocol of the search strategy can be viewed online (http://www.stempenoliumcutrecht.nl). An electronic search was performed using Medline, Embase, PsychInfo, National Institutes of Health, ClinicalTrials.gov, Cochrane Schizophrenia Group entries in PsiTri (http://psitri.stakes.fi), and the Cochrane Database of Systematic Reviews.

There were no year or language restrictions. The following basic search terms were used, both alone and in combinations: “schizophrenia,” “clozapine,” “resistant,” “refractory,” and the names of the particular pharmacological components used for augmentation. Additionally, the reference lists of the retrieved articles and relevant review articles were examined for cross-references. When necessary, corresponding authors were contacted to provide full details of study outcomes or scores for subgroups of patients treated with clozapine.

**Inclusion**

Consensus on the studies included was reached on the basis of the following criteria:

1. Randomized, double-blind placebo-controlled studies of at least 2 weeks duration regarding clozapine augmentation by a second drug.
2. Patients included had a diagnosis of a schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder, or psychotic disorder not otherwise specified), according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, or International Classification of Diseases-9 or 10).
3. Patients were treated with a stable dose of clozapine for a minimum of 4 weeks before the study started. The use of comedication was permitted if dosage had been without changes for 4 weeks prior to study onset and during the study.
4. Studies reported sufficient information to compute common effect size statistics, ie, means and SDs, exact \( P \), t, or \( z \) values (cf. Lipsey and Wilson) or corresponding authors could supply these data upon request.

Crossover studies were not excluded in order to obtain as much information as possible.

**Outcome Measures**

The primary outcome measure was the mean change in total score on the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS). Secondary outcome measures included positive and negative symptom subscores of the PANSS or the BPRS or scores on the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms. Patient data of the last observation carried forward were used for analysis. If studies did not provide these data and they could not be received from the corresponding authors, only the data of completers were used. Where possible, side effects were evaluated by comparing scores on the various side effects scales, weight, body mass index, hypersalivation, and...
prolactin blood levels between the augmentation and the placebo group.

**Statistical Analyses**

Two reviewers independently extracted data from the articles, any disagreements were resolved by consensus. Effect sizes were calculated for the mean differences (placebo vs augmentation) of the change score (end of treatment minus baseline) means and SDs. Change scores were used instead of pretreatment and posttreatment scores in order to avoid overestimation of the true effect size because of the pre-post treatment correlation. All effect sizes were calculated twice independently from the original articles to check for errors. When more than 1 RCT on a particular augmentation strategy was present, effect sizes of studies were pooled in meta-analyses to obtain a combined weighted effect size for primary and secondary outcome measures. Hedges’s *g* was used to quantify the mean weighted effect sizes of combined studies using a random model. A homogeneity statistic, *I*², was calculated to test whether the studies could be taken together to share a common population effect size. High heterogeneity (ie, *I*² 50% or higher) indicates heterogeneity of the individual study effect sizes, which poses a limitation to a reliable interpretation of the results. Values of *I*² between 30% and 50% were considered moderate. Outliers, defined as effect sizes that deviate more than 2 SDs from the mean weighted effect size, were removed from analyses. Effect sizes with a *P* < .05 were considered significant. All effect sizes were computed using Comprehensive Meta Analysis Version 2.0.

**Results**

Figure 1 reflects the literature search that resulted in 29 included RCTs. Data of a total of 1066 schizophrenia and schizoaffective patients were analyzed. Of the 29 included studies, 5 studies had a crossover design. Double-blind RCTs that could not be included are listed in online supplementary material (table 1) with the reason for exclusion.

**Antiepileptic Medication**

Eight studies applying antiepileptic drugs as clozapine augmentation were included, which are summarized in online supplementary material, for table 2.

**Lamotrigine.** For total symptom severity, lamotrigine showed superior efficacy to placebo, but heterogeneity was high. Figure 2 plots the individual effect sizes per study regarding total symptom score from the PANSS or BPRS rating scales. The study by Zoccali et al was considered an outlier and therefore excluded from analysis. After exclusion, the mean weighted effect size was no longer significant and studies were homogeneous.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Hedges’s g</th>
<th><em>p</em>-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiihonen et al. 2003</td>
<td>0.18</td>
<td>0.60</td>
</tr>
<tr>
<td>Kremer et al. 2004</td>
<td>0.44</td>
<td>0.45</td>
</tr>
<tr>
<td>Zoccali et al. 2007</td>
<td>1.32</td>
<td>0.00</td>
</tr>
<tr>
<td>Goff et al. 2007 (study 464)</td>
<td>0.15</td>
<td>0.73</td>
</tr>
<tr>
<td>Goff et al. 2007 (study 926)</td>
<td>0.38</td>
<td>0.22</td>
</tr>
<tr>
<td>Zoccali et al. 2007</td>
<td>0.53</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Fig. 2.** Meta-analysis of lamotrigine augmentation for total symptom score [positive and negative syndrome scale (PANSS)/brief psychiatric rating scale (BPRS)] including outlier.
The study by Afshar et al.\textsuperscript{57} was considered an outlier. After removal, the trend disappeared.

Regarding positive symptoms as measured by the subscale of the PANSS, topiramate was superior to placebo, but studies were heterogeneous. The study by Afshar et al.\textsuperscript{57} was considered an outlier. After exclusion, the significant effect disappeared and heterogeneity decreased. The effect of topiramate on severity of negative symptoms was not significant and studies were heterogeneous. However, the study by Afshar was not considered an outlier for this analysis. Statistical findings of these meta-analyses are summarized in table 1.

**Antidepressants**

Four studies concerning the efficacy of antidepressants as clozapine augmentation strategy were included. These studies are summarized in online supplementary material, table 3.

**Citalopram.** One RCT\textsuperscript{59} showed significantly superior efficacy of citalopram to placebo on total symptom severity. No significant difference was found between citalopram and placebo for positive PANSS subscores. However, citalopram was found to be superior to placebo regarding negative symptoms.

**Fluoxetine.** The RCT\textsuperscript{24} examining the efficacy of fluoxetine did not report PANSS total score. No significant differences were found between fluoxetine and placebo for positive symptom severity nor for negative symptoms.

**Mirtazapine.** A high mean weighted effect size was obtained regarding total symptom severity for mirtazapine; yet, significance was not reached (figure 4). There was very high heterogeneity among these studies for total symptom score as well as for negative symptoms. On both measures, Zoccali et al.\textsuperscript{60} showed large effect sizes, while Berk et al.\textsuperscript{61} did not. Detailed inspection of the methods applied in the 2 RCTs could not identify a reason for this extreme discrepancy.

No significant difference was found between mirtazapine and placebo for PANSS-positive score nor for negative symptom score. Heterogeneity for the positive symptoms was low. Statistical findings of these meta-analyses are summarized in table 1.

### Table 1. Summary of Augmentation Strategies and Their (Mean) Standardized Differences.

<table>
<thead>
<tr>
<th>Augmentation Strategy</th>
<th>Studies (N)</th>
<th>Subjects (N)</th>
<th>Hedges’s g</th>
<th>95% CI</th>
<th>g</th>
<th>95% CI</th>
<th>Positive Subscores</th>
<th>Hedges’s g</th>
<th>95% CI</th>
<th>g</th>
<th>95% CI</th>
<th>Negative Subscores</th>
<th>Hedges’s g</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiepileptics</td>
<td>7</td>
<td>189</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>5</td>
<td>143</td>
<td>0.53</td>
<td>0.03–1.04</td>
<td>60</td>
<td></td>
<td></td>
<td>0.38</td>
<td>−0.02 to 0.78</td>
<td>39</td>
<td>0.41</td>
<td>−0.13 to 0.94</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Minus outlier</td>
<td>4</td>
<td>92</td>
<td>0.27</td>
<td>−0.10 to 0.65</td>
<td>0</td>
<td></td>
<td></td>
<td>0.15</td>
<td>−0.22 to 0.52</td>
<td>0</td>
<td>0.12</td>
<td>−0.25 to 0.49</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>3</td>
<td>89</td>
<td>0.75</td>
<td>−0.05 to 1.56</td>
<td>69</td>
<td></td>
<td></td>
<td>0.63</td>
<td>0.03–1.23</td>
<td>47</td>
<td>0.66</td>
<td>−0.17 to 1.5</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Minus outlier</td>
<td>2</td>
<td>57</td>
<td>0.38</td>
<td>−0.13 to 0.89</td>
<td>0</td>
<td></td>
<td></td>
<td>0.39</td>
<td>−0.24 to 1.01</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
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<td>129</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Citalopram</td>
<td>1</td>
<td>61</td>
<td>0.81</td>
<td>0.30–1.33</td>
<td></td>
<td></td>
<td></td>
<td>0.28</td>
<td>−0.22 to 0.79</td>
<td>0.81</td>
<td>0.30–1.33</td>
<td></td>
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<td></td>
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<tr>
<td>Fluoxetine</td>
<td>1</td>
<td>33</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.12</td>
<td>−0.59 to 0.67</td>
<td>0</td>
<td>1.20</td>
<td>−0.25 to 2.66</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>2</td>
<td>35</td>
<td>2.91</td>
<td>−2.69 to 8.51</td>
<td>96</td>
<td></td>
<td></td>
<td>0.04</td>
<td>−0.59 to 0.67</td>
<td>0</td>
<td>1.20</td>
<td>−0.25 to 2.66</td>
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<tr>
<td>Antipsychotics</td>
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<td>548</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Amisulpride</td>
<td>1</td>
<td>20</td>
<td>0.13</td>
<td>−0.48 to 0.74</td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
<td>−0.50 to 0.72</td>
<td>0</td>
<td>0.21</td>
<td>−0.40 to 0.82</td>
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<tr>
<td>Aripiprazole</td>
<td>2</td>
<td>268</td>
<td>0.12</td>
<td>−0.12 to 0.36</td>
<td>0</td>
<td></td>
<td></td>
<td>0.22</td>
<td>−0.02 to 0.46</td>
<td>0</td>
<td>0.37</td>
<td>−0.19 to 0.93</td>
<td>74</td>
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</tr>
<tr>
<td>Haloperidol</td>
<td>1</td>
<td>6</td>
<td>−0.15</td>
<td>−1.51 to 1.21</td>
<td></td>
<td></td>
<td></td>
<td>0.26</td>
<td>−1.11 to 1.62</td>
<td>−0.31</td>
<td>−1.68 to 1.06</td>
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<td></td>
<td></td>
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<tr>
<td>Risperidone</td>
<td>5</td>
<td>226</td>
<td>0.18</td>
<td>−0.21 to 0.57</td>
<td>53</td>
<td></td>
<td></td>
<td>0.09</td>
<td>−0.24 to 0.74</td>
<td>56</td>
<td>0.22</td>
<td>−0.14 to 0.57</td>
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<tr>
<td>Sulpiride</td>
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<td>28</td>
<td>0.83</td>
<td>0.07–1.59</td>
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<td></td>
<td></td>
<td>0.77</td>
<td>0.02–1.52</td>
<td>0.76</td>
<td>0.01–1.51</td>
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<tr>
<td>Glutamatergics</td>
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<td></td>
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<tr>
<td>CX516</td>
<td>11</td>
<td>18</td>
<td>1.35</td>
<td>0.32–2.38</td>
<td></td>
<td></td>
<td></td>
<td>0.20</td>
<td>−0.74 to 1.14</td>
<td>1.43</td>
<td>0.38–2.46</td>
<td></td>
<td></td>
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<tr>
<td>D-cycloserine</td>
<td>1</td>
<td>11</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.40</td>
<td>−0.45 to 1.24</td>
<td>0.33</td>
<td>−0.52 to 1.17</td>
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<tr>
<td>D-serine</td>
<td>1</td>
<td>20</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.40</td>
<td>−0.45 to 1.24</td>
<td>0.33</td>
<td>−0.52 to 1.17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>3</td>
<td>68</td>
<td>−0.16</td>
<td>−0.62 to 0.30</td>
<td>0</td>
<td></td>
<td></td>
<td>−0.36</td>
<td>−1.19 to 0.46</td>
<td>67</td>
<td>−0.14</td>
<td>−0.60 to 0.32</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sarcosine</td>
<td>1</td>
<td>20</td>
<td>−0.21</td>
<td>−1.06 to 0.63</td>
<td>0</td>
<td></td>
<td></td>
<td>−0.07</td>
<td>−0.91 to 0.77</td>
<td>0.07</td>
<td>−0.91 to 0.77</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Note: Significant effects are indicated in bold. PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale.*
Antipsychotics

We included 10 studies concerning the efficacy of antipsychotic drugs as clozapine augmentation strategy, summarized in online supplementary material, table 4.

**Amisulpride.** One study\(^6^2\) on the efficacy of amisulpride in augmenting clozapine yielded no significant difference between amisulpride and placebo regarding total symptom severity. Amisulpride did not differ from placebo for positive symptoms nor for negative symptoms.

**Aripiprazole.** The 2 RCTs\(^6^6,6^7\) yielded no significant difference between aripiprazole and placebo for total symptom score (see figure 5). The degree of heterogeneity was low. In addition, no significant difference was found between aripiprazole and placebo for both the PANSS-positive and -negative scores. Concerning positive symptoms, studies were homogeneous. However, the degree of heterogeneity for the negative symptoms was high.

**Haloperidol.** No significant difference was observed between haloperidol and placebo regarding change in total symptom severity. In addition, haloperidol did not differ from placebo for positive nor for negative symptoms.

**Risperidone.** The overall effect size showed no significant difference between risperidone and placebo for total symptom score, with moderate to high heterogeneity, see figure 6. For positive symptoms, the meta-analysis showed no significant difference between risperidone and placebo. Heterogeneity among studies was high. The standardized mean difference regarding negative symptoms was not significant, with moderate heterogeneity among studies.

**Glycine.** The standardized mean difference for total symptom severity was not significant and studies were homogeneous (figure 7). The standardized mean difference for positive symptoms was not significant, with a high degree of heterogeneity. For negative symptom severity, the standardized mean difference was not significant, with low heterogeneity.

**Sarcosine.** No significant difference was observed between sarcosine and placebo regarding change in total symptom severity (positive and negative syndrome scale/brief psychiatric rating scale scores).

**CX516.** CX516 was superior to placebo on total symptom severity. Regarding positive symptom severity, no difference was found between CX516 and placebo. The effect on negative symptom severity was superior for CX516.

**d-cycloserine.** Only the scores on the negative subscales were provided, which yielded no significant difference.

**d-serine.** PANSS total scores were not provided. d-serine was not superior to placebo for positive symptoms nor for negative symptoms.

**Glutamatergic Drugs**

Seven studies concerning the efficacy of glutamatergic drugs in augmenting clozapine were included, summarized in online supplementary material, table 5.

**Sulpiride.** Sulpiride was superior to placebo in reducing total symptom severity. Regarding positive and negative symptoms, sulpiride was also superior to placebo. Statistical findings of these meta-analyses are summarized in table 1.
symptom severity. Concerning positive symptoms, sarcosine did not differ from placebo, nor for negative symptoms. Statistical findings of these meta-analyses are summarized in table 1.

**Side Effects**

Quantitative measures of side effects are listed in the online supplementary material, table 6. These data were too diverse to perform a meta-analysis. Qualitative inspection did not show consistently higher or lower side effects in the augmentation group.

**Discussion**

This study aimed to systematically review all available double-blind RCTs on pharmacological additions for clozapine-resistant patients with schizophrenia or schizoaffective disorder. We meta-analyzed 29 RCTs reporting on 15 different augmentation strategies that included 1066 patients in total. Better improvement of total symptom severity than placebo was found for lamotrigine, sulpiride, citalopram, and CX516 (a glutamatergic agonist). The superior efficacy of lamotrigine was only present if an outlier remained included in the meta-analysis. For sulpiride, citalopram, and CX516 results were retrieved from single RCTs. Significant better efficacy on positive symptom severity was found for topiramate and sulpiride. After outlier removal the significant effect for topiramate disappeared. Citalopram, sulpiride, and CX516 showed better efficacy for negative symptoms than placebo, all based on single studies.

Regarding clozapine augmentation with mood stabilizers, the significant effect size for lamotrigine was based on one study that deviated strongly from the others. The remaining 4 RCTs consistently showed no superior efficacy of lamotrigine than placebo. In a similar vein, the significant effect of topiramate on positive symptom severity depended on a single study with a strongly deviating finding. After exclusion of that study, topiramate was no longer superior to placebo. Thus, for both lamotrigine and topiramate, there is currently not enough evidence to regard these components as effective augmentation strategies for patients with insufficient response to clozapine. It is uncertain if this finding can be extrapolated to other mood stabilizing drugs. Small et al. compared addition of lithium with placebo in a double-blind study and observed improvement with lithium only for schizoaffective patients but not for patients with schizophrenia.

Augmentation with antidepressants did not improve total symptom severity, except for citalopram. While citalopram caused a larger decrease in negative symptom severity than placebo, this effect was not present for fluoxetine or mirtazapine. None of the three antidepressants showed a greater improvement of positive symptoms than placebo. The addition of a second antipsychotic drug to clozapine yielded negative results, with one exception. Aripiprazole was not better than placebo in decreasing total, positive, or negative symptoms nor was risperidone. Effects of amisulpride on all measurements were comparable to placebo, while sulpiride, a substance of pharmacological similarity, showed better improvement than placebo on total symptom severity and both positive and negative subscores. A possible explanation for this difference could be the short duration of the amisulpride trial. Another RCT on amisulpride augmentation, which did not meet inclusion criteria for this study, measured effects of 6 treatment weeks but also found no improvement in total symptom severity.

When the effects of glutamatergic drugs are summarized, the general picture shows similar effects than placebo on total symptom severity and on positive and negative subscores; CX516 being the only positive exception, with superior improvement on total symptom severity and negative symptom severity. However, as glutamatergic drugs are experimental, CX516 may not be a first choice in clinical practice.

Several other authors have reviewed augmentation strategies for clozapine, the majority of them concentrated on adding a second antipsychotic drug. Taylor and Smith meta-analyzed augmentation of clozapine with any second antipsychotic agents. They included 10 RCTs that showed marginally superior effect compared with placebo for total symptom severity. Barbui et al. reviewed antipsychotic addition to clozapine, which also included open-label studies. Congruent to our results, they found only modest or absent efficacy of augmentation. Kontaxakis et al. qualitatively reviewed all studies on risperidone addition to clozapine. Their results suggested that risperidone augmentation is an effective strategy for clozapine-resistant patients. However, their positive conclusion may result from the inclusion of case reports and open case series. Tiihonen quantitatively summarized the effect of lamotrigine addition, including the same studies as in this review. As they did not identify Zoccali et al. as an outlier, they arrived at a slightly more positive conclusion.

**Limitations**

The major limitation of this study is the relative small numbers of RCTs that could be included per drug. For some pharmacological substances, we could include single studies. This makes our database not robust against both type I and type II errors. The magnitude
of the effect sizes of therapeutic interventions in mental health can change considerably with the accumulation of new data,\(^\text{80}\) and some pharmacological augmentations may yield significant effect sizes on the appearance of new RCTs, while other (perhaps sulphpride) may decrease in effect size when more studies become available. A possibility to decrease the chance for type II errors would have to be pool studies on drugs with similar pharmacological mechanisms, such as SSRIs or amino acids that stimulate the N-methyl D-aspartate receptors. In this article, we decided to present results on single drugs, as findings from pooled meta-analyses are difficult to translate into clinical practice. In addition, many vaguely acquainted agents, such as topiramate and lamotrigine, differ to such a large extent in their mechanism of action that pooling would not lead to meaningful results.

In conclusion, the general picture emerges that there is currently no replicated evidence for any pharmacological augmentation strategy to combat resistant total, positive, or negative symptoms in clozapine-treated patients. All positive effects were either based on one outlying study or derived from a single RCT.

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**Supplementary Material**


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