Review

Clozapine augmentation strategies – a systematic meta-review of available evidence. Treatment options for clozapine resistance

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Abstract

Background: Treatment options for clozapine resistance are diverse whereas, in contrast, the evidence for augmentation or combination strategies is sparse.

Aims: We aimed to extract levels of evidence from available data and extrapolate recommendations for clinical practice.

Methods: We conducted a systematic literature search in the PubMed/MEDLINE database and in the Cochrane database. Included meta-analyses were assessed using Scottish Intercollegiate Guidelines Network criteria, with symptom improvement as the endpoint, in order to develop a recommendation grade for each clinical strategy identified.

Results: Our search identified 21 meta-analyses of clozapine combination or augmentation strategies. No strategies met Grade A criteria. Strategies meeting Grade B included combinations with first- or second-generation antipsychotics, augmentation with electroconvulsive therapy for persistent positive symptoms, and combination with certain antidepressants (fluoxetine, duloxetine, citalopram) for persistent negative symptoms. Augmentation strategies with mood-stabilisers, anticonvulsants, glutamatergics, repetitive transcranial magnetic stimulation, transcranial direct current stimulation or cognitive behavioural therapy met Grades C–D criteria only.

Conclusion: More high-quality clinical trials are needed to evaluate the efficacy of add-on treatments for symptom improvement in patients with clozapine resistance. Applying definitions of clozapine resistance would improve the reporting of future clinical trials. Augmentation with second-generation antipsychotics and first-generation antipsychotics can be beneficial, but the supporting evidence is from low-quality studies. Electroconvulsive therapy may be effective for clozapine-resistant positive symptoms.

Keywords

Schizophrenia, clozapine, augmentation, systematic review

Introduction

Between 20% and 30% of all patients with schizophrenia are treatment-resistant, with persistent symptoms following an adequate trial of antipsychotic medication (Hasan et al., 2012). Antipsychotic treatment resistance is defined as ongoing symptoms and functional impairment despite two adequate trials of different antipsychotics, with good adherence (Howes et al., 2017). Treatment resistance in schizophrenia contributes to a significant loss in patient's quality of life and is associated with a high economic burden (Kennedy et al., 2014). Clozapine is a highly effective second-generation antipsychotic (Chakos et al., 2001; Leucht et al., 2009a), reserved for treatment-resistant schizophrenia (TRS), and effective in reducing positive symptoms (Siskind et al., 2016), suicidal ideation (Meltzer et al., 2003; Meltzer and Okayli, 1995), aggressive behaviour (Volavka and Citrome, 2008), hospitalisations (Land et al., 2017) and overall mortality (Vermeulen et al., 2019). However, as many as 40% of patients with TRS fail to respond to clozapine (Siskind et al., 2017) and thus define a cohort of clozapine-resistant patients. Non-response or poor response to clozapine may occur despite 'adequate' clozapine blood levels (Porcelli et al., 2012; Tollefson et al., 2001) and 'adequate' treatment duration. A previous retrospective chart-review study and a secondary analysis have suggested that patients whose treatment with clozapine was delayed after a diagnosis of TRS gained less benefit from clozapine treatment (Ucok et al., 2015; Yoshimura et al., 2017). One possible reason for this delay in initiating such treatment might be underutilization of clozapine due to prescriber-related and institutional barriers as outlined elsewhere (Verdoux et al., 2018).

Clinical guidelines have different recommendations concerning an 'adequate' clozapine trial: whereas the PORT guidelines define a trial of clozapine as at least eight weeks at a dosage from 300–800 mg/day (with plasma levels above 350 ng/mL; Buchanan et al., 2010), the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines define 100–800 mg/

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day (again with plasma levels above 350 ng/mL; Hasan et al., 2012), the Treatment Response and Resistance in Psychosis (TRRIP) consensus group definition suggests at least three months with a minimum dosage of 500 mg/day (or serum levels above 350 ng/mL), since clozapine was only superior to other antipsychotics in a meta-analysis of head-to-head-comparisons at dosages above 400 mg/day (Howes et al., 2017; Leucht et al., 2009b). For clozapine-treated patients with persisting symptoms, pharmacological and non-pharmacological combination and augmentation strategies are well-established in clinical practice, although the available evidence for efficacy is sparse. As a consequence of disparate study designs, study quality and inclusion criteria, randomised controlled trials (RCTs) and meta-analyses with response or symptom reduction as primary outcomes show both positive and negative results for clozapine combination and augmentation strategies. Nevertheless, clozapine combination strategies with another first- or second-generation antipsychotic (FGA or SGA) or augmentation strategies with antidepressants (ADs), mood-stabilisers (MSs), anticonvulsants (ACs), glutamatergics or other agents are common practice to attempt to alleviate persisting positive or negative symptoms (Morrato et al., 2007). Electroconvulsive therapy (ECT) for persisting positive symptoms refractory to clozapine showed positive results in meta-analyses (Arumugham et al., 2016), but is accompanied by a relatively high rate of adverse events. Evidence for repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) as clozapine augmentation is limited due to a lack of high-quality RCTs (de Jesus et al., 2011) and the absence of meta-analytic data relevant to patients with clozapine-resistance. There have been three RCTs of effectiveness of cognitive behavioural therapy (CBT) for patients treated with clozapine, however these individual trials showed mixed results (Barretto et al., 2009; Morrison et al., 2018; Pinto et al., 1999) and, as one was published recently (Morrison et al., 2018), they have not yet been meta-analysed.

Prior reviews focusing on clozapine- resistance were either non-systematic (Miyamoto et al., 2014, 2015), focused exclusively on one or two classes of interventions (Ahmed et al., 2017; Barbui et al., 2009; Galling et al., 2017; Lally et al., 2016; Ortiz-Orendain et al., 2017; Singh and Singh, 2011; Taylor and Smith, 2009; Taylor et al., 2012; Veerman et al., 2014a, 2014b) or on a limited variety of mostly single drugs (Barber et al., 2017; Cipriani et al., 2009; Correll et al., 2017; Paton et al., 2007; Sommer et al., 2012a; Srisurapanont et al., 2015; Tiihonen et al., 2009; Veerman et al., 2014b; Wang et al., 2010; Zheng et al., 2016, 2017), did not cover all available clinical augmentation strategies including modern neurostimulation techniques or psychotherapeutic interventions (Buckley et al., 2001; Kontaxakis et al., 2005; Mouaffak et al., 2006; Muscatello et al., 2014; Porcelli et al., 2012), were older than 10 years (Chong and Remington, 2000; Remington et al., 2005; Tranulis et al., 2006), or covered all pharmacological and non-pharmacological treatment options without differentiating between low- and high-quality studies (Siskind et al., 2018).

We performed a systematic review of published systematic reviews with meta-analyses of interventions for patients with clozapine-resistant schizophrenia, considering outcomes of psychotic symptoms, aggression and suicide. We took into account recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (Moher et al., 2009), and the Scottish Intercollegiate Guidelines Network (SIGN) to summarise and evaluate all available evidence for the treatment of clozapine-resistant schizophrenia spectrum disorders, providing assessments of levels of scientific evidence and grades of recommendations.

Methods

Information sources and search

This meta-review was registered on PROSPERO (ID 1045*85*). Following the structure of the *International statistical classification of diseases and related health problems, 10th revision* (ICD-10 WHO Version, 2015), we searched the PubMed/MEDLINE database and the Cochrane database using the following search terms: 'psychosis AND clozapine' OR 'psychosis AND clozapine resistance' OR 'psychosis AND clozapine resistant' OR 'psychosis AND treatment resistance' OR 'psychosis AND treatment resistant' OR 'psychosis AND refractory' OR 'schizophrenia AND clozapine' OR 'schizophrenia AND clozapine resistance' OR 'schizophrenia AND clozapine resistant' OR 'schizophrenia AND treatment resistance' OR 'schizophrenia AND treatment resistant' OR 'schizophrenia AND refractory'. The literature searches and selection were performed by EW and AH. The titles and the abstracts of each citation were screened manually and the full text of each potentially relevant citation was retrieved for detailed review.

Eligibility criteria

The inclusion criteria were all meta-analyses and systematic reviews published in English between 1 January 1970 and 6 May 2018. One systematic review published in German (Zink and Dressing, 2005), one meta-analysis published in a Chinese journal (excluded on abstract level) (Wang et al., 2015), one meta-analysis published in Chinese (Li et al., 2016) and two meta-analyses published in Spanish (Jimenez-Cornejo et al., 2016; Kittsteiner Manubens et al., 2016) were excluded. The major exclusion criteria were: absence of meta-analytic data in the publication, and data not related to a clozapine add-on treatment option. Duplicate records were manually removed. We extracted meta-analytic data on the primary outcomes of psychotic symptom reduction and response among clozapine-treated subjects and, where possible, secondary outcomes of aggression and suicide. Selected meta-analyses are displayed in Table 1. Where possible, specific recommendations for clozapine-resistant categories of psychopathology (positive symptoms, negative symptoms, suicidal ideation and aggressive symptoms) were provided based on the single-drug results reported in the respective meta-analyses.

Data collection process

Meta-analytic data of the included publications was collected manually by EW and independently reviewed by LL. EW and LL extracted the data from the respective meta-analyses.

Risk of bias and summary measures

Each included meta-analysis was reviewed using the SIGN criteria. For each group of intervention agents, level of scientific

Table 1. Overview of the included systematic reviews/meta-analyses.

Meta-analysis (year)	Cases (*n* total) or min. and max. cases in the sub-analysis	Trials included (total)	Intervention	Statistical model (fixed or random effects), parameter	Primary outcome(s): response or symptom reduction or both	Level of evidence (SIGN)
Ahmed et al. (2017)	95 (CLZ+ECT)	9 (6 OL, 2 DB PC, 1 case series) for CLZ+ECT	CLZ+ECT vs ECT+FGA/SGA	random, SMD	symptom reduction	1–
Barbui et al. (2009)	1064 (OL) 227 (DB PC)	14 OL 6 DB PC trials	CLZ+FGA/SGA (single medication classes) vs CLZ (OL) CLZ+SGA (single medication classes) vs CLZ (DB PC)	random, SMD	symptom reduction, response	1+
Galling et al. (2017)	2073	20 (both OL and DB PC trials)	CLZ+FGA or +SGA vs CLZ	random, SMD	symptom reduction, response	1++
Singh and Singh (2011)	184	8 DB PC trials	CLZ+single glutamatergics vs CLZ	fixed, SMD	symptom reduction, response	1–
Siskind et al. (2018)	2223	Total: 46, only DB PC included	CLZ+single FGAs/SGAs/ADs/MSs/ACs, glutamatergics, other agents, CBT, ECT, rTMS	random, SMD	symptom reduction	1–
Correll et al. (2017)	57–1112 (analysis of meta-analyses)	3–20 (dependent on class of medication), meta-analyses of RCTs compared with controls (placebo/monotherapy) included	CLZ+ADs/single ACs/APs/single glutamatergic (glycine)	analysis of meta-analyses converted, SMD	symptom reduction	1+
Sommer et al. (2012a)	1066	10 for APs, 7 for ACs, 7 for glutamatergics, 4 for ADs, all DB PC trials	CLZ+single ACs/single ADs/single APs (FGA/SGA)/single glutamatergics	random, Hedge's g	symptom reduction	1+
Srisurapanont et al. (2015)	347	4, only DB PC trials	CLZ+ARI vs CLZ+PLC	IV, random, SMD	symptom reduction, response	1+
Taylor and Smith (2009)	522	10, only DB PC trials	CLZ+FGA/SGA vs CLZ+PLC	fixed, SMD	symptom reduction	1-
Taylor et al. (2012)	734	14, only DB PC trials	CLZ+FGA and SGA vs CLZ+PLC	fixed, SMD	symptom reduction	1+
Tiihonen et al. (2009)	161	5, only DB PC trials	CLZ+LTG vs CLZ+PLC	fixed, SMD	symptom reduction, response	1–
Veerman et al. (2014b)	394	13, only DB PC trials	CLZ+GLY, CLZ+LTG, CLZ+TOP	random, Hedge's g	symptom reduction	1–
Veerman et al. (2014a)	599 (for APs) 111 (for ADs) 79 (for others)	11 for APs, 4 for ADs, 4 small single studies for other agents, only DB, PC trials	CLZ+FGA/SGA CLZ+ADs CLZ+other agents (E-EPA, lithium, *Ginkgo biloba*)	random, Hedge's g	symptom reduction	1+
Zheng et al. (2017)	213–326	2–5 (dependent on single substance), only DB PC trials	CLZ+TOP, CLZ+LTG, CLZ+VLP	IV, random, SMD	symptom reduction, response	1–
Zheng et al. (2016)	213	4 RCTs	CLZ+TOP	random, SMD	symptom reduction	1–
Cipriani et al. (2009)	24–60 (dependent on combination)	2 RCTs	CLZ+RISP vs CLZ+SULP CLZ+ZIP vs CLZ+RISP	M-H, fixed, RR or M-H, fixed, RR	response, symptom reduction	1–

(Continued)

Table 1. (Continued)

Meta-analysis (year)	Cases (*n* total) or min. and max. cases in the sub-analysis	Trials included (total)	Intervention	Statistical model (fixed or random effects), parameter	Primary outcome(s): response or symptom reduction or both	Level of evidence (SIGN)
Barber et al. (2017)	105	5 RCTs in total	CLZ+ARI vs CLZ+HAL	IV, random, MD or M-H, random/fixed	response, symptom reduction	1–
	50		CLZ+AMI vs CLZ+QUE			
	60		CLZ+RISP vs CLZ+SULP			
	24		CLZ+RISP vs CLZ+ZIP			
	63		CLZ+ZIP vs CLZ+QUE			
Lally et al. (2016)	192	2 controlled trials, 4 OL, 2 retrospective chart reviews, 6 case series, 15 case reports	CLZ+ECT vs CLZ	random, response proportion	response	1–
Ortiz-Orendain et al. (2017)	1127	17 randomised and quasi-RCTs	CLZ+FGA or+SGA vs CLZ	M-H, random, RR	response	1–
Paton et al. (2007)	68	2 DB PC trials	CLZ+SULP/RISP vs CLZ	fixed, RR	response	1+
	98	2 DB PC trials	CLZ+RISP vs CLZ			
Wang et al. (2010)	221	1 DB PC trial, 1 OL, 2 RCTs	CLZ+SULP vs CLZ+/-PLC	M-H, fixed, RR or MD, IV, fixed, RR	response, symptom reduction	1–

AC: anticonvulsant; AD: anti-depressant medication; AP: antipsychotic medication; ARI: aripiprazole; CBT: cognitive behavioural therapy; CLZ: clozapine; DB: double-blind; ECT: electroconvulsive therapy; E-EPA: ethyl eicosapentaenoic acid; FGA: first-generation antipsychotic; GLY: glycine; HAL: haloperidol; IV: instrumental variable analysis; LTG: lamotrigine; MD: mean difference; M-H: Mantel-Haenszel; MS: mood-stabiliser; OL: open-label; PC: placebo-controlled; PLC: placebo; QUE: quetiapine; RCT: randomised controlled trial; RISP: risperidone; RR: risk ratio; rTMS: repetitive transcranial magnetic stimulation; SGA: second-generation antipsychotic; SIGN: Scottish Intercollegiate Guidelines Network; SMD: standard mean difference; SULP: sulpiride; TOP: topiramate; VLP: valproate; ZIP: ziprasidone.

evidence and grades of recommendations were assessed (Scottish Intercollegiate Guidelines Network, 2013).

Results

A total of 1066 records were identified in PubMed with no additional reviews identified in the Cochrane database. After removal of duplicates, 512 records remained. A total of 393 records were excluded on title/abstract level (see Figure 1). The remaining 119 studies were retrieved as full texts and were further assessed for eligibility. From these, 21 records were included in this meta-review. Ninety-eight records were excluded as they met at least one of the exclusion criteria at full text level (see Figure 1).

Study characteristics

From the 21 included meta-analyses/systematic reviews, nine focused exclusively on symptom reduction (Positive and Negative Syndrome Scale or Brief Psychiatric Rating Scale) (PANSS or BPRS) (Ahmed et al., 2017; Correll et al., 2017; Siskind et al., 2018; Sommer et al., 2012a; Taylor and Smith, 2009; Taylor et al., 2012; Veerman et al., 2014a, 2014b; Zheng et al., 2016), three focused exclusively on study-defined response (e.g. decrease >20 % in PANSS/BPRS scores) (Lally et al., 2016; Ortiz-Orendain et al., 2017; Paton et al., 2007) and nine focused on both outcomes (Barber et al., 2017; Barbui et al., 2009; Cipriani et al., 2009; Galling et al., 2017; Singh and Singh, 2011; Srisurapanont et al., 2015; Tiihonen et al., 2009; Wang et al., 2010; Zheng et al., 2017). When SIGN criteria were applied, one review was rated as 1++ with very little risk of bias (Galling et al., 2017), seven as 1+ with low risk of bias (Barbui et al., 2009; Correll et al., 2017; Paton et al., 2007; Sommer et al., 2012a; Srisurapanont et al., 2015; Taylor et al., 2012; Veerman et al., 2014a) and 13 as 1– with high risk of bias (Ahmed et al., 2017; Barber et al., 2017; Cipriani et al., 2009; Lally et al., 2016; Ortiz-Orendain et al., 2017; Singh and Singh, 2011; Siskind et al., 2018; Taylor and Smith, 2009; Tiihonen et al., 2009; Veerman et al., 2014b; Wang et al., 2010; Zheng et al., 2016; Zheng et al., 2017). No systematic review or meta-analysis investigated clozapine-resistant aggression or clozapine-resistant suicidality.

FGAs or SGAs

Fourteen reviews reported analyses of FGAs or SGAs as a clozapine add-on (Barber et al., 2017; Barbui et al., 2009; Cipriani et al., 2009; Correll et al., 2017; Galling et al., 2017; Ortiz-Orendain et al., 2017; Paton et al., 2007; Siskind et al., 2018; Sommer et al., 2012a; Srisurapanont et al., 2015; Taylor and Smith, 2009; Taylor et al., 2012; Veerman et al., 2014a; Wang et al., 2010). In the study reported by Galling et al. – the best rated according to SIGN criteria (1++) – clozapine plus first- or second-generation combination therapy was significantly superior to monotherapy in total symptom reduction (PANSS, BPRS) with an effect size (standard mean difference (SMD)) of −0.52 (n=612, 95% confidence interval (CI) (−0.899 to −0.142), p=0.007) when all studies (n=14) were included. This finding could not be replicated when only high-quality,

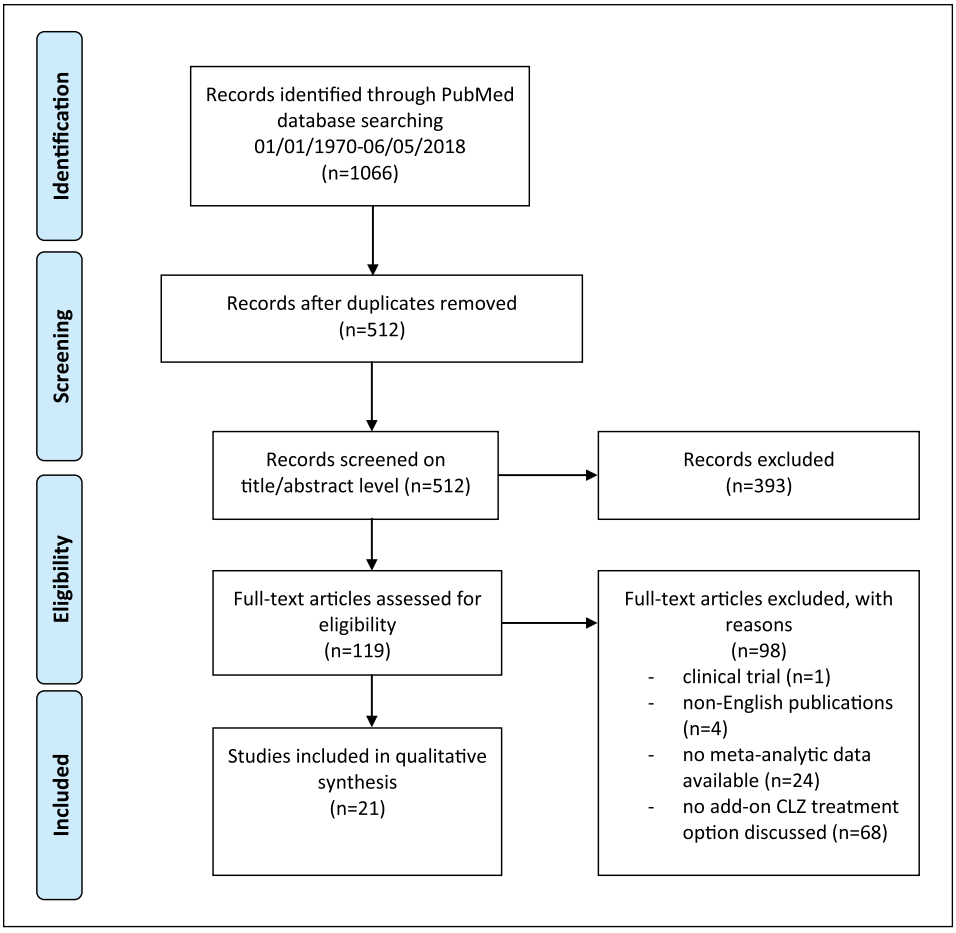

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flowchart of the applied search strategy according to PRISMA guidelines (Moher et al., 2009). CLZ: clozapine.

double-blind studies were included (SMD=−0.299, 95% CI (−0.783 to 0.185), p=0.226) (Galling et al., 2017). Rates of study-defined response were similar between clozapine combination- and clozapine monotherapy, and were clearly non-significant in double-blind and high-quality studies. In one meta-analysis and review including RCTs with aripiprazole, a dopamine D_2-receptor partial agonist, as clozapine add-on (N=152, number of trials (N) =3), aripiprazole had a favourable side-effect profile, associated with reduced clozapine-related adverse events, such as e.g. weight gain (mean difference) (95% CI) –1.36 kg (−2.35 to −0.36), p=0.008) (Srisurapanont et al., 2015). Based on SIGN criteria, a recommendation of grade B was given for clozapine augmentation with FGA or SGA (see Tables 2 and 3).

Antidepressants

Four reviews provided analyses of antidepressants as a clozapine add-on (Correll et al., 2017; Siskind et al., 2018; Sommer et al., 2012a; Veerman et al., 2014a). The studies of Correll et al. (2017) and Veerman et al. (2014a) were the best- rated according to SIGN criteria (1+) with aggregate analyses of augmentation with antidepressants as a group (fluoxetine, mirtazapine, duloxetine). Correll et al. undertook a meta-review of pharmacological augmentation of antipsychotic pharmacotherapy, and re-analysed meta-analytic data from Veerman et al. (2014a) for clozapine augmentation with antidepressants. Consistent with the results from Veerman et al., 2014a, Correll et al. (2017) did not observe a significant beneficial effect of augmentation on the total symptom score (n=78, N=3, SMD −2.02, 95% CI (–4.51 to 0.48), p=0.45), positive symptom score (n=111, N=4, SMD=−0.10, 95% CI (−0.49 to 0.28), p=0.60) or the negative symptom score (n=111, N=4, SMD=−0.87, 95% CI (–1.77 to 0.03), p=0.06) compared with clozapine monotherapy. Based on SIGN criteria, a recommendation grade B was given for clozapine augmentation with antidepressants (see Tables 2 and 3).

MSs or ACs

Eight reviews reported analyses of MSs or ACs as clozapine augmentation (Correll et al., 2017; Siskind et al., 2018; Sommer et al., 2012a; Tiihonen et al., 2009; Veerman et al., 2014a; Veerman et al., 2014b; Zheng et al., 2016, 2017). MSs were not analysed as a combined class in any of the included meta-analyses. Zheng et al. (2016, 2017), Siskind et al. (2018), Veerman et al. (2014b) and Tiihonen et al. (2009) were equally rated according to SIGN criteria (1–). Zheng

Table 2. Recommendations for pharmacological and non-pharmacological clozapine (CLZ) augmentation strategies based on Scottish Intercollegiate Guidelines Network (SIGN) criteria (Scottish Intercollegiate Guidelines Network, 2013).

Augmentation strategy CLZ+X[a]	Recommendation grade according to SIGN criteria (A–D) with symptomatic improvement as endpoint	LOE according to SIGN criteria	Comments
FGA	B	1++	Results for FGA as CLZ add-on significant only in low-quality studies (Galling et al., 2017). Thus, such combination must follow a strict risk-benefit evaluation and be reversed if no beneficial effect of the combination can be observed.
SGA	B	1++	Results for SGA as CLZ add-on significant only in low-quality studies (Galling et al., 2017). Thus, such combination must follow a strict risk-benefit evaluation and be reversed if no beneficial effect of the combination can be observed.
Antidepressants	B	1+	Fluoxetine as CLZ-add-on is superior to CLZ monotherapy both for positive (Siskind et al., 2018) and negative symptoms (Siskind et al., 2018), but since fluoxetine increases CLZ plasma levels, effects might be related to elevated CLZ plasma levels. Additionally, results only significant in low quality studies, further no significant effects shown in Sommer et al., 2012a for both positive and negative symptoms. Duloxetine as CLZ-add-on superior to CLZ-monotherapy for negative symptoms (Siskind et al., 2018), in Veerman et al., 2014a, positive results only in aggregate analysis of antidepressants, not as single substance; citalopram as CLZ add-on was superior to CLZ monotherapy for persistent negative symptoms in one small RCT for negative symptoms of Chinese origin (Lan et al., 2006, *n*=61) analysed in one meta-analysis (Sommer et al., 2012a); negative evidence for mirtazapine (Siskind et al., 2018; Sommer et al., 2012a)
MS/AC (valproate, lithium, lamotrigine, topiramate)	C	1-	(Sodium-) valproate is effective in current meta-analyses as CLZ add-on for CLZ-persistent positive symptoms (Siskind et al., 2018; Zheng et al., 2017) despite negative results in systematic reviews with valproate as add-on in schizophrenia (Basan and Leucht, 2004; Wang et al., 2016). According to available meta-analytic data, (sodium-) valproate seems to be more effective than other MS/ACs for CLZ-resistant positive symptoms, however this data is only from low quality studies. Positive evidence sparse for Lithium as CLZ add-on for positive symptoms (Siskind et al., 2018), however this data is from low quality studies; significant negative effects of lithium reported in Veerman et al., 2014a, no significant effects reported on positive and overall symptoms in Veerman et al., 2014a; inconsistent evidence for topiramate as CLZ add-on: superior to CLZ monotherapy for positive symptoms in Siskind et al., 2018; Sommer et al., 2012a and for positive and negative symptoms in Zheng et al., 2016 and Zheng et al., 2017 (same Topiramate cohorts of *n*=213 in both publications) vs not superior to CLZ monotherapy in Correll et al., 2017; Veerman et al., 2014b both for positive and negative symptoms; inconsistent evidence for lamotrigine as CLZ add-on: superior to CLZ-monotherapy for positive and negative symptoms in Tiihonen et al., 2009 and superior for total symptoms in Sommer et al., 2012a vs not superior to CLZ-monotherapy for positive and negative symptoms in Zheng et al., 2017; Veerman et al., 2014b; Correll et al., 2017; Siskind et al., 2018. A level of evidence of 1– was chosen, since only one meta-analysis focuses sufficiently on lithium as CLZ augmentation strategy (Siskind et al., 2018, 1–, *n*=118), and two meta-analyses on valproate as CLZ add-on (Siskind et al., 2018, 1-; Zheng et al., 2017, 1-) with negative systematic reviews focusing on valproate as adjunct for schizophrenia (Basan and Leucht, 2004; Wang et al., 2016). When combining CLZ with a MS or AC, possible interaction effects and an increase in side-effects must be taken into account.
Glutamatergics	D	1+	There is inconsistent evidence for glutamatergics. There is some evidence for glycine for positive symptoms (Correll et al., 2017; Siskind et al. 2018; Veerman et al. 2014b), however there is evidence for augmentation with memantine being significantly superior to clozapine monotherapy for negative symptoms (Singh and Singhet, 2011; Siskind et al., 2018), but when Siskind et al. restricted included studies to those that used rating scales to define clozapine resistance, the results were no longer significant. In general, the available data is too inconsistent to give a recommendation for clinical practice.
ECT	B	1-	Best evidence for CLZ-resistant positive symptoms (Lally et al., 2016) and CLZ-resistant suicidality after a close risk-/benefit assessment due to an elevated risk for adverse events. Recommendation grade B was chosen, since ECT is the most effective last resort treatment for CLZ-resistant patients with persistent positive symptoms in current clinical practice and as the safety profile in this difficult clinical situation is acceptable.

(Continued)

Table 2. (Continued)

Augmentation strategy CLZ+X[a]	Recommendation grade according to SIGN criteria (A–D) with symptomatic improvement as endpoint	LOE according to SIGN criteria	Comments
rTMS	C	2+	Low evidence as effective CLZ add-on treatment, more favourable side-effect profile compared to ECT, potential add-on for CLZ-resistant positive and negative symptoms (Siskind et al., 2018), a level of evidence of 2+ was chosen, since only one meta-analysis includes rTMS as CLZ augmentation strategy with a low case number (Siskind et al., 2018) based on a RCT from de Jesus et al., 2011 (*n*=17); Other existing rTMS-meta-analyses do not investigate CLZ-refractory populations.
tDCS	D	-	No evidence available, no clinical data for CLZ-resistant patients available
CBT	D	1-/1+	No superiority for CBT as CLZ add-on treatment, neither for positive nor for negative symptoms (Siskind et al., 2018, 1–). One well-conducted randomised trial (1+) from Morrison et al. (*n*=487) that has not yet been included in meta-analyses showed negative results for CBT as CLZ add-on for total symptoms; evidence is still low due to a lack of studies/meta-analyses investigating CLZ-resistant negative symptoms.

AC: anticonvulsant; CBT: cognitive behavioural therapy; ECT: electroconvulsive therapy; FGA: first-generation antipsychotic; LOE: level of evidence; MS: mood-stabiliser; RCT: randomised controlled trial; rTMS: repetitive transcranial magnetic stimulation; SGA: second-generation antipsychotic; tDCS: transcranial direct current stimulation.

[a]The grouping of antipsychotics into FGAs and SGAs is in line with the meta-analysis by Galling et al., 2017. In this study, no single substance analyses were performed. The substances for FGAs were: fluphenazine, pimozide and sulpiride. The substances for SGAs were: aripiprazole, paliperidone, risperidone, sertindole and ziprasidone. The group MS/AC contains valproate, lithium, lamotrigine and topiramate according to Table 2 that were investigated only as single substances in available meta-analyses (Correll et al., 2017; Siskind et al., 2018; Sommer et al., 2012a; Tiihonen et al., 2009; Veerman et al., 2014a; Veerman et al., 2014b; Zheng et al., 2016, 2017). The group of antidepressants contains fluoxetine, duloxetine and citalopram analysed as single substances according to available meta-analyses (Siskind et al., 2018; Sommer et al., 2012a; Veerman et al., 2014a). Glutamatergics are investigated as single substances in available meta-analyses (Correll et al., 2017; Singh and Singhet, 2011; Siskind et al., 2018; Veerman et al., 2014b).

et al. (2017) analysed clozapine augmentation with (sodium) valproate in placebo-controlled trials, noting that (sodium) valproate-augmentation of clozapine was significantly superior for total symptom scores (PANSS/BPRS) (n=326, N=5, SMD=–1.26, 95% CI (−2.05 to −0.47), p=0.002) and positive symptom scores (PANSS/BPRS) (n=326, N=5, SMD=−0.78, 95% CI (–1.36 to 0.20), p=0.009) compared with clozapine monotherapy. After removing two outliers (SMD<–1.0), results remained significant (SMD=−0.60, 95% CI (−0.88 to −0.32), $p<0.0001$). No significant result was reported for negative sub-scores (PANSS/BPRS) (SMD=−0.26, 95% CI (−0.55 to 0.03), p=0.08). Regarding study-defined response, described as a reduction in PANSS total score of at least 50% (two RCTs) or BPRS total score reduction of at least 30% (one RCT), the pooled effect of three RCTs showed that (sodium-) valproate was not associated with a significant difference compared with clozapine monotherapy risk ratio =1.36, 95% CI (0.91 to 2.03), p=0.13). All five included trials were of Chinese origin and four were of poor quality. No significant differences regarding adverse drug reaction were reported concerning valproate as a clozapine add-on. Overall, these results are consistent with the article from Siskind et al. (2018) reporting positive effects of valproate as clozapine add-on for total psychosis symptoms (n=118, N=2, SMD=2.36, 95% CI (−3.96 to −0.75), but also including two low-quality trials.

Siskind et al. (2018) investigated lithium as clozapine add-on and found significant improvements in positive in one low-quality RCT for positive symptoms (n=59, N=1, SMD=−0.52, 95% CI (–1.04 to −0.00), $p<0.05$) and total symptoms (n=59, N=1, SMD=−2.13, 95% CI (−2.78 to –1.49), $p<0.05$), but not for negative symptoms (n=59, N=1, SMD=−0.05, 95% CI (−0.57 to 0.46)). Adverse events were not specifically investigated in this study. Veerman et al., 2014a reported only results for lithium as clozapine add-on in one small RCT (see footnote in Table 4). Since the meta-analysis by Veerman et al. 2014 was not mainly focused on mood-stabilizers, this meta-analysis was rated elsewhere (see "Antidepressants" and "FGAs or SGAs"). The best-rated article on ACs as clozapine add-on (1+) (Correll et al., 2017), investigated single AC substances (lamotrigine and topiramate) as clozapine add-ons, and found these were not significantly superior in total, positive and negative symptom scores. Based on SIGN criteria, a recommendation grade C was given for clozapine augmentation with MSs or ACs (see Tables 2 and 4).

Glutamatergic agents

Five studies analysed glutamatergic agents as clozapine add-on (Correll et al., 2017; Singh and Singh, 2011; Siskind et al., 2018; Sommer et al., 2012a; Veerman et al., 2014b). The best-rated studies (1+) from Sommer et al. (2012a) and Correll et al. (2017) analysed single glutamatergic agents. Correll et al. found significant superiority for glycine as a clozapine add- on augmentation strategy for positive symptoms (n=68, N=3, SMD=−0.64, 95% CI (–1.11 to −0.17), p=0.01), but not for negative or total symptoms (n=57, N=3, SMD=−0.16 95% CI (−0.61 to 0.29), p=0.60; n=68, N=3, SMD=−0.07, 95% CI (−0.52 to 0.38), p=0.07 respectively). Adverse drug reactions were not investigated.

Table 3. Pharmacological combination and augmentation strategies (antipsychotics and antidepressants). Results from meta-analyses investigating single substances on persistent positive, negative and total symptoms.

Drug	NbN mode of action	Sommer et al., 2012a (1+)	Veerman et al., 2014a (1+)	Siskind et al., 2018 (1–)
Positive symptoms				
Amisulpride	Receptor antagonist (D2)	ns (*N*=20)	Ø	ns (*N*=28)[a]
Aripiprazole	Receptor partial agonist (D2, 5-HT1A), Receptor antagonist (5-HT2A)	ns (*N*=268)	ns (*N*=297)	ns (*N*=328)
Haloperidol	Receptor antagonist (D2)	ns (*N*=6)	ns (*N*=6)	Ø
Olanzapine	Receptor antagonist (D2, 5-HT2)	Ø	Ø	ns (*N*=50)
Pimozide	Receptor antagonist (D2)	Ø	ns (*N*=28)	ns (*N*=53)
Risperidone	Receptor antagonist (D2, 5-HT2,NE alpha-2)	ns (*N*=226)	ns (*N*=188)	ns (*N*=144)
Sertindole	Receptor antagonist (D2, 5-HT2)	Ø	ns (*N*=50)	ns (*N*=50)
Sulpiride	Receptor antagonist (D2)	++ (*N*=28)	++ (*N*=28)	Ø
Negative symptoms				
Amisulpride	Receptor antagonist (D2)	ns (*N*=20)	Ø	ns (*N*=85)[a]
Aripiprazole	Receptor partial agonist (D2, 5-HT1A), Receptor antagonist (5-HT2A)	ns (*N*=268)	ns (*N*=297)	++ (*N*=328)
Haloperidol	Receptor antagonist (D2)	ns (*N*=6)	ns (*N*=6)	Ø
Olanzapine	Receptor antagonist (D2, 5-HT2)	Ø	Ø	++ (*N*=50)
Pimozide	Receptor antagonist (D2)	Ø	ns (*N*=28)	ns (*N*=53)
Risperidone	Receptor antagonist (D2, 5-HT2, NE alpha-2)	ns (*N*=226)	ns (*N*=188)	ns (*N*=144)
Sertindole	Receptor antagonist (D2, 5-HT2)	Ø	ns (*N*=50)	ns (*N*=50)
Sulpiride	Receptor antagonist (D2)	++ (*N*=28)	++ (*N*=28)	Ø
Total symptoms				
Amisulpride	Receptor antagonist (D2)	ns (*N*=20)	ns (*N*=16)	ns (*N*=85)[a]
Aripiprazole	Receptor partial agonist (D2, 5-HT1A), receptor antagonist (5-HT2A)	ns (*N*=268)	ns (*N*=297)	++ (*N*=486)
Haloperidol	Receptor antagonist (D2)	ns (*N*=6)	ns (*N*=6)	ns (*N*=100)
Olanzapine	Receptor antagonist (D2, 5-HT2)	Ø	Ø	ns (*N*=50)
Penfluridol	Receptor antagonist (D2)	Ø	Ø	++ (*N*=80)
Pimozide	Receptor antagonist (D2)	Ø	ns (*N*=28)	ns (*N*=53)
Risperidone	Receptor antagonist (D2, 5-HT2,NE alpha-2)	ns (*N*=226)	ns (*N*=188)	ns (*N*=144)
Sertindole	Receptor antagonist (D2, 5-HT2)	Ø	ns (*N*=50)	ns (*N*=50)
Sulpiride	Receptor antagonist (D2)	++ (*N*=28)	++ (*N*=28)	Ø
Positive Symptoms				
Citalopram	Reuptake inhibitor (SERT)	ns (*N*=61)	Ø	Ø
Duloxetine	Reuptake inhibitor (SERT and NET)	Ø	Ø	ns (*N*=33)
Fluoxetine	Reuptake inhibitor (SERT)	ns (*N*=33)	Ø	++ (*N*=269)
Mirtazapine	Receptor antagonist (NE alpha-2, 5-HT2, 5-HT3)	ns (*N*=35)	Ø	ns (*N*=35)
Paroxetine	Reuptake inhibitor (SERT)	Ø	Ø	++ (*N*=66)
Negative symptoms				
Citalopram	Reuptake inhibitor (SERT)	++ (*N*=61)	Ø	Ø
Duloxetine	Reuptake inhibitor (SERT and NET)	Ø	Ø	++ (*N*=33)
Fluoxetine	Reuptake inhibitor (SERT)	ns (*N*=33)	Ø	++ (*N*=269)
Mirtazapine	Receptor antagonist (NE alpha-2, 5-HT2, 5-HT3)	ns (*N*=35)	Ø	ns (*N*=35)
Paroxetine	Reuptake inhibitor (SERT)	Ø	Ø	++ (*N*=66)
Total symptoms				
Citalopram	Reuptake inhibitor (SERT)	++ (*N*=61)	Ø	Ø
Duloxetine	Reuptake inhibitor (SERT and NET)	Ø	Ø	++ (*N*=33)
Fluoxetine	Reuptake inhibitor (SERT)	Ø	Ø	++ (*N*=296)
Mirtazapine	Receptor antagonist (NE alpha-2, 5-HT2, 5-HT3)	ns (*N*=35)	Ø	ns (*N*=35)
Paroxetine	Reuptake inhibitor (SERT)	Ø	Ø	++ (*N*=66)

5-HT: 5-hydroxytryptamine; D2: Dopamine D2; NE: norepinephrine; NET: norepinephrine transporter; SERT: serotonine transporter.
++: significant; Ø: not reported/no data; *N*: number; NbN: neuroscience-based nomenclature; ns: not significant.
[a]Sulpride and amisulpride were analysed as one substance in the meta-analysis by Siskind et al., 2018.

Table 4. Pharmacological augmentation strategies (mood-stabiliser and anticonvulsants). Results from meta-analyses investigating single substances on persistent positive, negative and total symptoms.

Drug	NbN mode of action	Correll et al., 2017 (1+)	Sommer et al., 2012a (1+)	Siskind et al., 2018 (1–)	Veerman et al., 2014b (1–)	Zheng et al., 2017 (1–)
Positive symptoms						
Lamotrigine	Voltage-gated sodium channel blocker	ns (*n*=185)	ns (*n*=143)	ns (*n*=85)	ns (*n*=185)	ns (*n*=291)
Lithium[a]	Enzyme interactions	Ø	Ø	++ (*n*=59)	Ø	Ø
Sodium valproate	Yet to be determined	Ø	Ø	++ (*n*=118)	Ø	++ (*n*=326)
Topiramate	Facilitation of GABA transmission, receptor antagonist on AMPA and KA	ns (*n*=152)	++ (*n*=89)	++ (*n*=43)	ns (*n*=152)	++ (*n*=213)
Negative symptoms						
Lamotrigine	Voltage-gated sodium channel blocker	ns (*n*=185)	ns (*n*=143)	ns (*n*=85)	ns (*n*=185)	ns (*n*=291)
Lithium	Enzyme interactions	Ø	Ø	ns (*n*=59)	Ø	Ø
Sodium valproate	Yet to be determined	Ø	Ø	ns (*n*=118)	Ø	ns (*n*=326)
Topiramate	Facilitation of GABA transmission, receptor antagonist on AMPA and KA	ns (*n*=152)	ns (*n*=89)	++ (*n*=43)	ns (*n*=152)	++ (*n*=213)
Total symptoms						
Lamotrigine	Voltage-gated sodium channel blocker	Ø	++ (*n*=143)	ns (*n*=85)	ns (*n*=185)	ns (*n*=291)
Lithium	Enzyme interactions	Ø	Ø	++ (*n*=59)	Ø	Ø
Sodium valproate	Yet to be determined	Ø	Ø	++ (*n*=118)	Ø	++ (*n*=326)
Magnesium Valproate	Yet to be determined	Ø	Ø	Ø	Ø	Ø
Topiramate	Facilitation of GABA transmission, receptor antagonist on AMPA and KA	Ø	ns (*n*=89)	ns (*n*=43)	ns (*n*=152)	++ (*n*=213)

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CGI: Clinical Global Impression Score; GABA: gamma-aminobutyric acid: KA: kainic acid; PANSS: Positive and Negative Syndrome Scale.

++: significant; Ø: not reported/no data; *n*: number; NbN: neuroscience-based nomenclature; ns: not significant; RCT: randomised controlled trial.

[a]Veerman et al. (2014a) reported the results of a single small RCT combining lithium with clozapine in 10 schizophrenia and 10 schizoaffective patients (Small et al., 2003). No positive effect of this combination was detected for schizophrenia patients, but schizoaffective patients improved on CGI and PANSS total and negative scales (Small et al., 2003).

There is evidence for augmentation with memantine being significantly superior to clozapine monotherapy for negative symptoms in publications from Siskind et al. (2018) (*n*=134, *N*=3, SMD=−0.56, 95% CI (−0.93 to −0.20), $p<0.05$) and Singh and Singh (2011) (*n*=21, *N*=1, SMD=−3.09, 95% CI not reported, *p*=0.00). When Siskind et al. restricted included studies to those that used rating scales to define clozapine- resistance, the results were no longer significant.

Sommer et al. found significantly better efficacy than placebo on total symptom severity and negative symptoms for CX516, a glutamatergic agonist, but these findings were based on one small single study (for total symptoms: *n*=18, *N*=1, Hedge's g=1.35, 95% CI (0.32 to 2.38); for negative symptoms: Hedge's g=1.43, 95% CI (0.38 to 2.46)). Qualitative inspection of side-effect rates did not show consistently higher or lower side effects in the augmentation group. Based on SIGN criteria, a recommendation grade D was chosen for clozapine augmentation with glutamatergic agents (see Table 2).

ECT

Three studies analysed ECT as clozapine augmentation (Ahmed et al., 2017; Lally et al., 2016; Siskind et al., 2018). The highest-rated review Lally et al. (2016) (1–) had the largest number of included studies, and reported the proportion of responders to clozapine plus ECT in RCTs, and open-label trials. By pooling data from 71 people across four open-label trials (*n*=32) and one RCT (*n*=39), the pooled proportion of response to clozapine+ECT was 54% (95% CI (21.8 to 83.6%)). Response rates to treatment were measured by a pre-defined reduction in total BPRS, PANSS or Clinical Global Impression scores. The included studies and case reports together demonstrated an overall response rate to clozapine plus ECT of 66% (95% CI (57.5–74.3%), 83 out of 126 patients). In all studies, adverse events were relatively high, at 14% of identified cases (24 out of 166 patients). Based on SIGN criteria, a recommendation grade B was given for clozapine augmentation with ECT (see Table 2).

rTMS

One article analysed rTMS as a clozapine augmentation (Siskind et al., 2018). The publication from Siskind et al. found no superiority for rTMS augmentation, but since only one small trial was included evidence on this strategy is limited (for total symptoms: *n*=17, *N*=1, SMD=−0.71, 95% CI (–1.70 to 0.28), for positive symptoms: *n*=17, *N*=1, SMD=0.15, 95% CI (−0.80 to 1.10); for negative symptoms: *n*=17, *N*=1, SMD=−0.67, 95% CI (–1.65 to 0.32). Based on SIGN criteria, a recommendation grade C was given for clozapine augmentation with rTMS (see Table 2).

tDCS

No publication investigated tDCS as a clozapine add-on. For this reason, no level of evidence could be provided. A

recommendation grade D was given due to this lack of clinical data (see Table 2).

CBT

One article analysed CBT as a clozapine add-on (Siskind et al., 2018), finding no superiority for CBT augmentation among clozapine patients in the one included RCT (for total symptoms: *n*=21, *N*=1, SMD=−0.07, 95% CI (−0.94 to 0.79); for positive symptoms: *n*=21, *N*=1, SMD=0.24, 95% CI (−0.63 to 1.11); for negative symptoms: *n*=21, *N*=1, SMD=−0.07, 95% CI (−0.80 to 0.93)). Based on SIGN criteria, a recommendation grade D was chosen for clozapine augmentation with CBT (see Table 2).

Aggression/suicide

No included meta-analyses provided data on clozapine augmentation vs control for aggression or suicide as an outcome. As such, no recommendations could be provided for clozapine augmentation strategies for these outcomes.

Discussion

Given the sparse and at times contradictory evidence for clozapine augmentation, we aimed to investigate the quality of evidence for clozapine augmentation from existing meta-analyses and to develop clinical recommendations. Following a systematic literature review we were able to include 21 reviews in our qualitative analysis. The quality of the included meta-analyses was variable, with some of the included meta-analyses mixing co-initiation and augmentation studies (Barbui et al., 2009), failing to differentiate between low- and high-quality studies (Taylor et al., 2012), or appeared prone to a high risk of bias. Some meta-analyses and systematic reviews included small trials and single drug combinations in their analyses, limiting a meaningful interpretation of results (Barber et al., 2017; Cipriani et al., 2009; Singh and Singh, 2011; Siskind et al., 2018; Sommer et al., 2012a; Wang et al., 2010). Generalisability was further hampered by an absence of a research definition of clozapine-resistance or ultra-resistant schizophrenia, and by the diversity of durations of included trials.

When only high-quality studies with a sufficient number of participants were included, most meta-analyses reported no beneficial effect of pharmacological augmentation strategies, particularly for first/second generation antipsychotics. Table 3 displays the effects of antipsychotics and antidepressants and Table 4 the effects of MSs and ACs investigated as single substances (defined following the neuroscience-based nomenclature (NbN)) (Nutt and Blier, 2016) on positive, negative and total symptoms in latest meta-analyses.

ECT seems to be an effective non-pharmacological clozapine add-on strategy, however this is based on only one high-quality study from Petrides et al. (2015) (*n*=39) that showed high efficacy of ECT as an add-on to clozapine. There is some concern that ECT added to clozapine is accompanied by an increased risk of side effects (compared to other neurostimulation techniques) including prolonged seizures or cognitive dysfunctions (Arumugham et al., 2016; Lally et al., 2016), although this is inconsistent with a mirror image study suggesting that the safety profile of ECT in schizophrenia is acceptable (Lin et al., 2018).

Although the higher quality meta-analyses included in our review did not find clozapine augmentation with antidepressants to be superior to controls, one major meta-analysis from Helfer et al. (*n*=3608), not specifically investigating clozapine-refractory patients but schizophrenia patients with depressive or negative symptoms in general, found that adjunctive antidepressants have small beneficial effects on those symptoms with a low risk of exacerbation of psychosis and adverse effects (Helfer et al., 2016). Sodium valproate as clozapine add-on may be promising, but most of this data is from low-quality trials. Furthermore, results for valproate as adjunct to antipsychotic (non-clozapine) medication were negative in two well-conducted systematic reviews and meta-analyses among schizophrenia patients (Basan and Leucht, 2004; Wang et al., 2016). Valproate augmentation was associated with a number of adverse events among which sedation and dizziness appeared significantly more frequently than in the control groups (Wang et al., 2016).

Trials using non-invasive brain stimulation and CBT trials among clozapine patients are scarce, so evidence from RCTs with larger sample sizes is warranted. The trial from de Jesus et al. (2011) that was included in the meta-analysis by Siskind et al. (2018) focused on persistent positive symptoms with rTMS as clozapine add- on strategy. The trial from Barretto et al. (2009) that was included in the same meta-analysis (Siskind et al., 2018) is, so far, the only CBT augmentation study (*n*=21) of clozapine-refractory schizophrenia patients included in a meta-analysis, showing no significant improvements in the general psychopathology, positive and negative symptom scores. The trial from Pinto et al. (1999) is a co-initiation study of clozapine and CBT and therefore cannot be considered as augmentation. The recently published high-quality randomised assessor-blinded trial from Morrison et al. (*n*=487) (Morrison et al., 2018) investigated the effect of CBT in clozapine-resistant patients (clozapine at a stable dose of 400 mg or more-unless limited by tolerability-for at least 12 weeks). When compared with treatment as usual, there was no difference in the primary endpoint of PANSS total scores at 21 months. Still, CBT is a treatment option for schizophrenia patients with persistent symptoms in order to reduce associated emotional distress and anxiety and offer symptom coping strategies (Pontillo et al., 2016; Sommer et al., 2012b).

In summary, ECT, FGA/SGA combination and fluoxetine augmentation strategies are assessed as Grade B for clozapine-resistant positive symptoms. (Sodium-)valproate, lithium, lamotrigine and topiramate as augmentation options are assessed as Grade C along with rTMS for clozapine-resistant positive symptoms (see Table 2). For clozapine-resistant negative symptoms, FGA/SGA combination, fluoxetine, duloxetine and citalopram are assessed as Grade B. Lamotrigine and topiramate along with rTMS are assessed as Grade C (see Table 2). However, Table 3 shows that the overall beneficial effect of adding an antipsychotic or an antidepressant cannot be attributed with good evidence to a specific compound and that the recommendations are based on the whole class. No meta-analysis included information on clozapine-refractory aggression/hostility or clozapine-refractory suicidality. Furthermore, functional and psychosocial outcomes such as quality of life are under-investigated among clozapine-refractory patients. One meta-analysis investigated the suicidal

risk during clozapine treatment and observed that long-term treatment with clozapine was associated with three-fold overall reduction of risk of suicidal behaviours (Hennen and Baldessarini, 2005). One systematic review from Frogley et al. found evidence from RCTs, non-controlled and retrospective studies that the anti-aggressive effect of clozapine was more marked in those with a treatment-resistant illness course (Frogley et al., 2012).

Future clozapine-augmentation RCTs should preferably define clozapine resistance and focus on non-pharmacological interventions in order to create reliable evidence for these under-investigated strategies, including neurostimulation and CBT. Symptomatic and functional outcomes should be assessed in order to obtain reliable data on other potential beneficial effects of clozapine augmentation strategies.

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